Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Ipilimumab (rch)

Proprietary Product Name: Yervoy/ Winglore

Sponsor: Bristol-Myers Squibb Australia Pty Ltd

February 2017

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

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

About AusPARs

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

Contents

List of the most common abbreviations used in this AusPAR

Abbreviation	Meaning
ACPM	Advisory Committee on Prescription Medicines
AE	adverse event
ASCO	American Society of Clinical Oncology
BLOQ	below limit of quantitation
BORR	best overall response rate
BRAFmt	BRAF mutant
BRAFwt	BRAF wild-type (not mutated)
CI	confidence interval
CL	clearance
C_{minss}	steady-state trough concentration
CR	complete response
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DTIC	dacarbazine
EAP	expanded access protocol
ECOG	Eastern Cooperative Oncology Group
eGFR	Estimated glomerular filtration rate
E_{max}	maximum effect
EMA	European Medicines Agency
ER	exposure response
ER-OS	exposure-response overall survival
ER-irAE	exposure-response immune related adverse event
ESMO	European Society for Medical Oncology

Abbreviation	Meaning
EU	European Union
FAQ	frequently asked questions
GCP	good clinical practice
GI	gastrointestinal
GIT	gastrointestinal tract
gp 100	A synthetic peptide cancer vaccine consisting of amino acid residues 209 through to 217 of the glycoprotein 100 (gp 100) melanoma antigen with a methionine substitution at position 210.
HAHA	human anti-human antibody
HR	hazards ratio
hr	hour
IBE	Immune Breakthrough Events
imARs	immune mediated adverse reactions
irAE	immune related adverse event
irAR	immune related adverse reaction
IRC	independent review committee
irCA	immune related clinical activity
IV	intravenous
LDH	lactate dehydrogenase
M	Monotherapy
NCCN	National Comprehensive Cancer Network
Ob	Observational
OS	overall survival
PCR	polymerase chain reaction
PD	pharmacodynamics
PFS	progression free survival
pg	page

Abbreviation	Meaning
PI	product information
PK	pharmacokinetics
PopPK	population pharmacokinetics
PR	partial response
PSURs	Periodic safety update reports
SAE	serious adverse event
SmPC	Summary of Product Characteristics
TA	tumour assessment
TPN	Total parenteral nutrition
ULN	upper limit of normal
US	United States (of America)
VC	volume of central compartment
Vd	Volume of distribution
wk	week
WT	body weight

I. Introduction to product submission

Submission details

Type of submission:	Major variation (new indication)
Decision:	Approved
Date of decision:	30 March 2015
Date on ATRG	9 April 2015
Active ingredient:	Ipilimumab (rch)
Product names:	Yervoy, Winglore
Sponsor's name and address:	Bristol-Myers Squibb Australia Pty Ltd PO Box 1080 Mount Waverly VIC 3149
Dose form:	Injection , concentrated
Strengths:	200 mg in 40 mL and 50 mg in 10 mL
Containers:	10 ml or 40 mL glass vial
Pack sizes:	One 10 mL glass vial (50 mg size) One 40 mL glass vial (200 mg size)
Approved therapeutic use:	*Yervoy, as first line therapy for patients with unresectable or metastatic melanoma*
Route of administration:	intravenous
Dosage:	3 mg/kg IV for a maximum of 4 doses
ARTG numbers:	174322, 174327, 174319, 174326

Product background

This AusPAR describes the application by the sponsor to register Yervoy/ Winglore ipilimumab for the following indication

> *As first line therapy for patients with unresectable or metastatic melanoma.*

Ipilimumab at the time of this application was currently registered for the indication

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

Yervoy is currently provided as a concentrate solution for injection and the current and proposed dose is 3 mg/kg intravenously for a maximum of 4 doses.

Ipilimumab (rch) is a recombinant, fully human monoclonal antibody directed against cytotoxic T-lymphocyte antigen-4 (CTLA-4). Ipilimumab is a IgG1 kappa immunoglobulin and is produced in mammalian (Chinese hamster ovary) cell culture. CTLA-4 is a key

regulator of T cell activity. Ipilimumab is a CTLA-4 immune checkpoint inhibitor. Binding of ipilimumab to CTLA-4 results in blockage of an inhibitory signal, and therefore enhances T cell response to tumour antigens. CTLA-4 blockade can also reduce T regulatory cell function, which may lead to an increase in anti-tumour immune response.

Gp100 is a synthetic peptide cancer vaccine consisting of amino acid residues 209 through 217 of the glycoprotein 100 (gp100), the melanoma antigen, with a methionine substitution at position 210. This experimental vaccine was used in some of the studies described in this AusPAR.

Agents which are currently registered in Australia for the treatment of unresectable /metastatic melanoma include dacarbazine, temozolomide and fotemustine.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 4 July 2011.

Overseas regulatory history

At the time the TGA considered this application; a similar application for Yervoy as a first line therapy had been approved or was submitted as is outlined in Table 1.

Table 1: Overseas regulatory status Yervoy (ipilimumab) first line indication

Country/region	Submission date /approval date	Details/indication
European Union Centralised Procedure)	-/ 31 Oct 2013	Yervoy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.
United States of America	-/ 25 Mar 2011	Yervoy (ipilimumab) is indicated for the treatment of unresectable or metastatic melanoma.
Canada	18 Nov 2013/ 10 Sept 2014	Yervoy (ipilimumab) is indicated for the treatment of unresectable or metastatic melanoma.
Switzerland	15 Jan 2014/ 10 Nov 2014	Yervoy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults
Singapore	-/ 29 Aug 2014	Yervoy (ipilimumab) is indicated for the treatment of unresectable or metastatic melanoma.
Israel	-/ 09 Jul 2013	Yervoy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults

Country/region	Submission date /approval date	Details/indication
South Korea	-/ 05 Dec 2014	Yervoy (ipilimumab) is indicated for the treatment of unresectable or metastatic melanoma.
South America Argentina Chile Colombia Brazil Peru	 -/ 26 Oct 2011 -/ 30 Nov 2011 -/ 30 Apr 2012 -/ 11 Jun 2012 -/ 12 Jul 2013	Yervoy (ipilimumab) is indicated for the treatment of unresectable or metastatic melanoma

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

Metastatic melanoma is a disease that has previously lacked therapeutic options which provide meaningful survival benefit, with a median overall survival (OS) of 6 to 9 months without treatment. The global incidence and mortality of the disease is increasing. The standard of care for systemic therapy has included dacarbazine (DTIC), fotemustine, or interleukin-2 (IL-2), none of which provide any survival advantage. Identification of defining BRAF mutant (BRAFmt) molecular subtype in approximately 50% of melanomas has permitted successful development of targeted therapeutic options.

Recently both targeted (BRAF/MEK inhibitors) and immunomodulatory (ipilimumab) therapies have been approved in the US and EU for the treatment of patients with

advanced disease, on the basis of significantly improved overall survival benefit. In MDX010-20, ipilimumab improved OS by 32 to 34% (hazard ratios (HRs) 0.68 and 0.66) and median OS by approximately 4 months for the two ipilimumab containing groups compared with the gp100 control group. The long term survival effect of ipilimumab was reflected in the estimated 1 year and 2 year survival rates, which were consistently higher for the ipilimumab containing treatment groups relative to the gp100 group. The estimated 2 year survival rate was 24% among subjects in the 3 mg/kg ipilimumab group, compared with 14% in the control group. Furthermore, with respect to therapy targeting BRAFmt, the development of resistance is common. Currently in Australia, ipilimumab is approved for use as monotherapy at a 3 mg/kg dosing for a maximum of 4 doses for use in patients who have un-resectable stage III or IV melanoma.

The current application seeks to extend the indication for treatment of metastatic melanoma with ipilimumab from the second line setting (after prior therapy), to the first line setting (treatment naive patients), *'for the treatment of advanced (un-resectable or metastatic) melanoma in adults*' at the 3 mg/kg posology.

The application has been made on the basis of the unmet need for effective therapeutic options for previously untreated patients with advanced melanoma. The rationale proposed by the sponsor in support of this application includes; the provision of durable survival advantage provided by the drug for untreated patients in one Phase III study using a 10 mg/kg dosing administered concurrently with dacarbazine (DTIC), the survival advantage provided for previously treated patients in one pivotal Phase III study using a 3 mg/kg posology (MDX010-20, previously evaluated), the survival benefit provided by the 3 mg/kg dosing schedule for previously treated and untreated patients from pooled analyses, the propensity for resistance development for targeted therapies, and the ongoing need for therapeutic options for patients with BRAF wild type (BRAFwt, not mutated) tumours.

Comment: With respect to the sponsor's rationale for the application described above, whilst the clinical need does exist for more effective therapeutic options for previously treated and untreated patients with advanced melanoma (irrespective of mutational status), the majority of submitted data reference in support of the rationale is not directly relevant to the proposed usage in the application. The referenced studies described above include those with a different posology (10 mg/kg), different treatment schedule (combination therapy), include maintenance treatment (compared to monotherapy) and evaluates a population that differs from that in the application. Thus, the submitted data does not meet the guidelines of good statistical principles of clinical trial conduct with limited external validity.

Guidance

Pre-submission advice was sought from the sponsor at a meeting held on 7th September 2012.

Feedback was sought regarding the suitability of the data for the 3 mg/kg dosing in untreated patients with advanced melanoma from previously submitted studies, in support of the application for extension of indication of the drug to the first line setting.

The sponsor's proposed strategy was to submit bridging data, rather than conduct a randomised clinical trial in the patients identified in the proposed indication.

The key TGA recommendations were (with minor typographical amendments):

1. The TGA recommended that the sponsor provide additional data in addition to the 35 untreated subjects described in the background document to increase the sample size of previously untreated patients who received 3 mg/kg. The TGA stated preference

for randomised data however in discussion they indicated that anything that increases the sample size, including uncontrolled data or even observational data from commercially treated US patients, would be helpful.

TGA would need evidence to demonstrate that the baseline characteristics from MDX010-020, CA184-024 and the bridging populations are similar.

2. In addition the TGA stated that the sponsor has to decide if the strength of the existing bridging justification is sufficient to file the submission now. BMS confirmed we believe that the existing bridging justification is adequate. Based on this bridging data, the 1st line Type II variation was submitted to EMA on 31 July was accepted by the EMA and validated on the 17th August.

Comment: These referenced dates appear to be in 2012, given the timing of the pre-submission meeting, although this is not clearly stated. Approval for the extension of indication was obtained in the EU on 31 October, 2013.

3. The bridging strategy is a possible way to expand the indication to include 1st line patients. TGA acknowledged that Study CA184-024 was a well conducted study. TGA reviewers stated that the bridging justification must be sufficiently strong for them to accept the 3 mg/kg dose. However, the strength of the justification would be a matter for evaluation.

In line with all of the recommendations from the TGA, the sponsor deferred the current application to provide addition supportive evidence in the untreated population from two additional retrospective studies (CA184332, CA184338), and the baseline characteristics of subjects enrolled in studies MDX010-020 and CA184-024 are described in the dossier.

Data specifically addressing the recommendations in the pre-submission meeting include the following. In the pre-submission meeting notes, one recommendation from the TGA was that the baseline characteristics of patients from MDX010-020, CA184-024 and the bridging populations should be shown to be similar. This has been demonstrated by the sponsor utilising comparisons between the two Phase III studies, observational studies and the pooled chemotherapy naive population.

In the "clinical overview cumulative safety" the sponsor describes the similarities between overall survival (OS) rates obtained for patients investigated within studies using a 3 mg/kg posology, which is superior to that obtained by DTIC alone. These studies and this analysis have been discussed in Section 7of Attachment 2, with particular reference to data contained on Table 27 Attachment 2. Comparison was also made to a number of historical benchmarks.

Contents of the clinical dossier

There were no studies included in the dossier that investigated the treatment schedule of the proposed usage in the appropriate population for the current application.

The clinical dossier focused on the provision of new and collated data supportive of the efficacy of the drug in the treated and untreated population, at both the 3 mg/kg and 10 mg/kg dosing, as combination therapy and as monotherapy, with other additional information in support of proposed changes to the PI.

The majority of the new data submitted is summarised in Table 2 according to relevance to pharmacokinetics, pharmacodynamics, efficacy, and safety.

Table 2: Summary of major individual data sources submitted for clinical evaluation

Report	Phase	Prior systemic therapy	Treatment schedule	Dose mg/kg	PK/PD	Efficacy (end point)	Safety	Comment
CA184078	I	No	M+C	10	x	Secondary	x	-
CA184024	III	No	C	10	x	Primary	x	-
CA184042	II	Yes	M	10	-	Primary	x	-
MDX10-16	II	Yes	M+C	Mixed	-	Adjuvant setting	x	Terminated prematurely
CA184045	EAP	Yes	M	Mixed	-	Exploratory only for 10 mg/kg	x	Dosing changed, Interim
CA184332	Ob	No	M	3	-	Primary	x	Interim, post marketing
CA184338	Ob	No	M	3	-	Primary	x	Interim, post marketing
PopPK report	Mixed	Mixed	Mixed	Mixed	x	ER-OS	E-irAE	-

'x' indicates relevant data is present; '-' no data is present. Combination (C) Extended Access Program (EAP) Monotherapy (M) Observational (Ob) Pharmacokinetics (PK) Pharmacodynamics (PD) Population pharmacokinetics PK (PopPK), (ER-OS) exposure-response overall survival, irAE: immune related adverse event

Three Completed Clinical Study Reports;

- Phase III CA184024 (Mod5351) for efficacy, safety and pharmacokinetic data for ipilimumab 10 mg/kg in combination with DTIC, with a maintenance phase
- Phase II CA184042 (Mod 5352) for efficacy, and safety for ipilimumab 10 mg/kg monotherapy (with a maintenance phase) for patients with brain metastases with or without concurrent steroid use
- Phase I CA184078 (Mod 5342) pharmacokinetic, pharmacodynamic, safety data and secondary efficacy data of ipilimumab 10 mg/kg monotherapy and as combination therapy (all with a maintenance phase).

Comment: The sponsor indicates that CA184024 and CA184078 are 'pertinent' to the claimed indication. However these studies utilise a different posology, combination therapy and a maintenance schedule in contrast to the current

application. Furthermore, the latter study has small numbers (n = 59) and has a Phase I design. Thus, these studies provide limited relevant evidence.

Three Abbreviated Clinical Study Reports (synopses);

- MDX010-16 provides safety, and early efficacy data for use of ipilimumab in the adjuvant setting in a prematurely terminated study (Mod 5353). This study was terminated early following the sponsor's acquisition of Medarex, where the clinical development program had evolved to use of a different ipilimumab treatment schedule and focused on monotherapy rather than concomitant administration with gp100
- Retrospective observational studies in the first line setting CA184332 and CA184338 (Mod 536).

One interim summary

- CA184045 safety and efficacy of expanded access program (EAP) using ipilimumab 10 mg/kg (Mod 5352).

One Population pharmacokinetics (PopPK) report

- PopPK analysis of combined Studies (CA184004, CA184007, CA184008, CA184022, CA184024, CA184078), with investigation of exposure response (ER) in the untreated and treated patients (Mod 5335, report named as '930057648').

Others reports with data

- Line listing of cumulative serious adverse events. The report indicates that the key (legend for abbreviations) is provided on the final page of the report but is not found there, or in the Clinical Overview documents
- Supportive data for of immune-mediated adverse event analysis for United States PI for previously evaluated Studies MDX010-20, CA184004, CA184022 (5353 supportive data).

Protocols included without clinical data

- CA184029 protocol (5351), CA184025 revised protocol (5352), CA184089 EU guidelines for the expanded access (Mod 5352).

Paediatric data

The submission did not include paediatric data.

Good clinical practice

Declaration of the study being performed in accordance to GCP with ethics approval is included in the report of CA184024, CA184042, CA184078, MDX10-16, CA184045 and for all studies referred to within this submission that were previously evaluated.

The two observational Studies CA184332 and CA184338 did not require patient consent for treatment. The reports included the following declaration of compliance with the Guideline.[1]

CA184089 EU expanded access program requires patient consent consistent with institutional requirements.

[1] International Society for Pharmacoepidemiology (ISPE) Guidelines for Good Pharmacoepidemiology Practices (GPP) and applicable regulatory requirements.

Pharmacokinetics

Studies providing pharmacokinetic data

Summaries of the new pharmacokinetic studies were provided. The exposure-response overall survival (ER-OS) data from the PopPK report which assessed patient data from CA184024 was also provided.

Table 3 shows the studies relating to each pharmacokinetic topic and the location of each study summary. The summary of studies with data used in the PopPK analysis presented in Table 3.

Table3: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID
PK in healthy adults	General PK- Single dose	NA
	- Multi-dose	NA
	Bioequivalence† - Single dose	NA
	Multi-dose	NA
	Food effect	NA
PK in special populations	Target population § - Single dose	
	- Multi-dose	CA184078 PopPK
	Hepatic impairment	CA184078 (mild)# PopPK (mild)
	Renal impairment	CA184078 (mild)~ PopPK (mild to mod)
	Neonates/infants/children/adolescents	NA
	Elderly	NA
Genetic/gender-related PK	Males versus females	PopPK
PK interactions	Carboplatin/paclitaxel	CA184078
	Dacarbazine	CA184078 PopPK
Population PK analyses	Healthy subjects	NA
	Target population	CA184078 PopPK

PK topic	Subtopic	Study ID
	Other	NA

* Indicates the primary aim of the study. † Bioequivalence of different formulations. § Subjects who would be eligible to receive the drug if approved for the proposed indication. # total bilirubin 1.0 to 1.5 times ULN or AST > ULN as defined using the National Cancer Institute criteria of hepatic dysfunction ~ GFR: mild (GFR < 90 and > 60 mL/min/1.73 m^2; n = 349), moderate (GFR < 60 and > 30 mL/min/1.73 m^2; n = 82)

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

Table 4: Ipilimumab clinical studies contributing to PK data and PopPK modelling

Population (monotherapy or with chemotherapy)	Study Number	Study Characteristics	Dose of Ipilimumab, Route of Administration and (Formulation)[a]	# of Subjects Contributing PK Samples
Untreated and previously treated advanced melanoma	CA184004[4]	Phase 2, multi-center, study randomized to two doses of ipilimumab	3 mg/kg and 10 mg/kg, IV[b] (Process B-5000L, 5 mg/mL)	79 subjects with sparse PK
Untreated and previously treated advanced melanoma	CA184007[5]	Phase 2, multi-center, study wherein subjects received 10 mg/kg ipilimumab and were randomized (double-blind) to concurrent oral budesonide or placebo	10 mg/kg, IV[b] (Process B-5000L, 5 mg/mL)	112 subjects with sparse PK (15 with intensive PK)
Previously treated advanced melanoma	CA184008[6]	Phase 2, multi-center, open label study	10 mg/kg, IV (Process B-5000L 5 mg/mL)	148 subjects with sparse PK (5 with intensive PK)
Previously treated advanced melanoma	CA184022[7]	Phase 2, multi-center, study randomized (double-blind) to three doses of ipilimumab	0.3 mg/kg, 3 mg/kg, 10 mg/kg, IV (Process B-5000L, 5 mg/mL)	159 subjects with sparse PK
Untreated advanced melanoma	CA184024[2]	Phase 3, randomized, double-blind, multi-center, study wherein subjects receiving dacarbazine plus 10 mg/kg of ipilimumab vs. dacarbazine with placebo	10 mg/kg, IV (Process B-5000L, 5 mg/mL)	240 subjects with sparse PK
Untreated advanced melanoma	CA184078[8]	Phase 1, randomized, parallel, 3-arm study to characterize the effects of ipilimumab on the PK of chemotherapy (dacarbazine; carboplatin-paclitaxel) and the effects of chemotherapy (dacarbazine; carboplatin-paclitaxel) on the PK of ipilimumab in subjects with untreated advanced melanoma	10 mg/kg, IV (Process B-5000L, 5 mg/mL)	59 subjects with intensive PK
Untreated advanced melanoma	MDX010-08[9]	Phase 2, open label, randomized study of ipilimumab with and without dacarbazine	3 mg/kg, IV (Process A: 5 mg/mL)	31 subjects with sparse PK
Previously treated advanced melanoma	MDX010-15[10]	Phase 1, open-label clinical pharmacology study of escalating single and repeat doses of ipilimumab	3 mg/kg (Process A, 5 mg/mL) 2.8 to 20 mg/kg (Process B-350L, 5 mg/mL)	68 intensive PK
Previously treated advanced melanoma	MDX010-20[3]	Phase 3, randomized, double-blind, multicenter study comparing ipilimumab alone, ipilimumab in combination with gp100 peptide vaccine, or gp 100 peptide vaccine alone.	3 mg/kg, IV for four doses (Process B-350L and Process B-5000L: 5 mg/mL)	No PK measurements

[a] See Quality Overall Summary[11] for more detailed information regarding the manufacturing processes (Processes A and B)

[b] IV = Intravenous as a 90-min infusion

Evaluator's conclusions on pharmacokinetics

There were no studies included in the dossier that investigated the treatment schedule of the proposed usage in the appropriate population for the current application.

The PopPK analysis was performed by the sponsor to provide PK data for ipilimumab monotherapy at 3 mg/kg dose in untreated patients. There were no studies analysed or submitted in the dossier that included randomised data utilising the treatment schedule of the proposed usage in the relevant population for the current application. In contrast to the current application, studies analysed in the PopPK report included pre-treated patients, those administered 10 mg/kg and those treated with combination therapy. Furthermore, all studies included a maintenance phase (or a re-induction phase) in contrast to the proposed usage. The PopPK analysis collated data from the newly submitted studies and previously evaluated Studies (CA184004, CA184007, CA184008, CA184022, CA184024, and CA184078). The summary of studies utilised in the PopPK analysis are summarised in Table 4.

The new PK data incorporated into the submitted PopPK report was provided in this submission from Studies CA184078 and CA184024, of which both used a 10 mg/kg posology. Furthermore, CA184024 investigated ipilimumab administration in combination with DTIC. Total numbers investigated in CA184078 were small (n = 59) with only 20 out of 59 patients receiving ipilimumab monotherapy (10 mg/kg). Whilst individual data was presented in the CA184078 clinical study report (CSR), PK data for CA184024 (n = 240) was presented embedded within the PopPK analysis performed by the sponsor. Of particular note, approximately 50% of PK data from CA184078 was not used in the PopPK modelling (only n = 29 out of 59 included).

The previously submitted studies with PK data consisted of four Phase II studies: (CA184004: n = 79, CA184007: n = 112, CA184008: n = 148 and CA184022: n = 177). These were also evaluated in a previously submitted PopPK analysis.

Thus, the newly submitted PopPK analysis which derived data from these heterogeneous studies, acts as an extension of the previous analysis, with new data predominantly sourced from one Phase III study using ipilimumab 10 mg/kg in combination with DTIC. With reference to the current application, of a total of 785 patients analysed, 528 out of 785 (67%) received ipilimumab monotherapy (versus DTIC + ipilimumab), and 348 out of 785 (44%) were previously untreated. All studies included a maintenance phase in contrast to the proposed usage. With respect to posology, 58 patients were dosed at 0.3 mg/kg, 101 patients at 3 mg/kg, and 626 patients at 10 mg/kg. Only 14 previously untreated patients received ipilimumab 3 mg/kg monotherapy, pertinent to the application. Please see Table 25 of Attachment 2 for the contribution of numbers for previously untreated patients administered ipilimumab 3 mg/kg monotherapy, according to study. Note should be made that all studies included a maintenance phase. Only patients from CA184024 (10 mg/kg + DTIC) were included in the ER-OS analysis. For the final exposure safety immune related adverse event (irAE) analysis, 58 patients were dosed at 0.3 mg/kg, 101 patients at 3 mg/kg, and 626 patients at 10 mg/kg.

Table 4 (above) outlines the different manufacturing processes (A or B), dosing schedules (0.3 mg/kg, 3 mg/kg, 10 mg/kg, or in combination with DTIC), and different number of PK samples (intensive versus sparse). Time points for PK sample collection times may differ between each study. For example, intensive sampling was obtained in one PK drug-drug interaction study (CA184078) and a subset of subjects with advanced melanoma who received multiple doses of ipilimumab (CA184007 and CA184008). Sparse PK samples were analysed from CA184004, CA184007, CA184008, CA184022 and CA184024, of which different dosing schedules were investigated. Note should be made that the populations investigated were not uniform between studies. Specifically, inclusion and exclusion criteria for studies were not the same.

Similar to the previous PopPK analysis, the sponsor considered that the comparison of predicted values with observed values provided external validation of the model. For the ER-OS and the irAE analysis, no external validation of results was performed.

The external PopPK evaluator found that the assessment of the methods, results and discussion of the sponsor's report, which included a repeat of the PopPK models, confirmed the results presented. Specifically, methodology utilised for the analysis was confirmed to be appropriate and in accordance with the guidelines.

Pharmacodynamics

Table 5 shows the studies relating to each pharmacodynamic topic.

Table 5: Submitted pharmacodynamic studies

PD Topic	Subtopic	Study ID
Primary Pharmacology		No studies
Secondary Pharmacology	Effect on absolute lymphocyte count (ALC)	CA184078 CA184024
Gender other genetic and Age-Related Differences in PD Response	Effect of gender	No studies
	Effect of age	No studies
PD Interactions		No studies
Population PD and PK-PD analyses	Healthy subjects	No studies
	Target population	No studies

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

Please see Attachment 2 for full details of the clinical evaluator's assessment of the PK data.

CA184078

Comment: The study design, and conduct were satisfactory. However, with respect to the current application, no PK data is presented in this study that addresses the proposed usage.

CA184024

Within the CSR no PK information is provided beyond a listing of serum concentrations and the study analysis/data is embedded into the PopPK report.

Briefly, CA184024 was a randomised, double blind, multi centre, Phase III study in untreated subjects with un-resectable Stage III or IV melanoma receiving DTIC plus placebo or DTIC plus 10 mg/kg of ipilimumab. Ipilimumab was administered as 4 single doses as 90 minute IV infusions at Weeks 1, 4, 7 and 10 (treatment period) in combination with DTIC treatment. Subjects who were eligible for extended doses in the maintenance period received the same doses of ipilimumab on Weeks 24, 36, 48 and every 12 weeks on study thereafter until unacceptable toxicity, tumour progression or withdrawal of consent. Sparse PK data from 240 subjects were obtained in this study; but non-compartmental analysis (NCA) PK parameters were not estimated in CA184024, as only 7 data points were collected across a 12 week interval over 4 treatment induction doses.

Population pharmacokinetic report

A separate PopPK evaluation was prepared for this submission. An extract from that report is provided in Attachment 2.

The discussion of the report addresses how well the final models describe the data and the clinical relevance of any covariate influences in detail. The results of the PopPK analysis have been related to previously obtained results and are in agreement with them. The discussion of the report meets the EMEA guidelines.

Explicit discussion points for the PopPK model have been:

- PK of ipilimumab is linear in the dose range tested.
- The PK of ipilimumab is time invariant.
- No difference in the PK of ipilimumab in previously untreated versus previously treated patients.
- Ipilimumab should be dosed according to the total body weight of the patient, due to the significant impact of total body weight (WT) on ipilimumab clearance (CL) found, effecting overall exposure to the drug.
- Ipilimumab CL increases with increasing baseline lactate dehydrogenase (LDH). However patients with sufficiently high LDH to cause clinical meaningful changes in CL have been found to be rare and are unlikely to have clinically meaningful impact of LDH on their ipilimumab CL.
- Renal function and mild hepatic impairment have no impact on ipilimumab CL.
- Dacarbazine did not affect ipilimumab CL.

All of the above claims have been supported by rigorous evaluation of the model and model outcomes. The claim of PK being time invariant and linear over the tested dose range is adequate and appropriate. The most clinical influential covariates found were total body weight on CL and volume of distribution (Vd), both increase with increasing weight and the patient with the smallest weight and the largest weight in the study population had significantly smaller and larger CL, respectively, compared to the average weight patients in the study population. In particular, steady-state trough concentration (C_{minss}) concentrations have been linked to efficacy and safety of ipilimumab. It has been shown that a fixed dose for all patients will underexpose heavier patients leading potentially to treatment failure. Vice versa, overexposure in lighter patients might lead to increased risk of adverse events. The conclusion dosing of ipilimumab based on patient's body weight is appropriate.

The impact of LDH on ipilimumab CL has been discussed and it was concluded that baseline LDH values less than 675 IU/L are unlikely to have clinically meaningful impact on ipilimumab CL, and that the additional increase in CL in patients with LDH values as high as 5 x upper limit of normal (ULN) is only approximately 10% relative to patients with LDH of 3 x ULN. It should also be noted that LDH is a key prognostic factor indicating worse outcomes; consequently this may lead to a higher ipilimumab CL, in higher risk patients and should be considered when these are being treated. It is however not discussed in further details if dose changes should be recommended in high risk patients.

Renal function and mild hepatic impairment showed to have no clinically relevant effect on ipilimumab CL. Estimated glomerular filtration rate (eGFR) was included in the final model however, the explorations of the effect magnitude showed that ipilimumab CL changed by less than 20% for the lowest and highest eGFR in comparison to the population median value. The effect of hepatic impairment on ipilimumab CL is based mainly on a comparison between patients with normal hepatic function and mild

impairment. The effect of hepatic impairment should be revaluated again in future studies when more data from patients with moderate to severe impairment are available.

Additionally, the influence of concomitant therapy with Dacarbazine, immunogenicity (human anti-human antibody (HAHA) status) and patient's age were discussed and found not to be clinically relevant predictors of ipilimumab CL. These are appropriate conclusions given the results of the PopPK analysis.

The PopPK model predicted that 3 and 10 mg/kg doses yield pharmacologically active ipilimumab C_{minss} values when the target trough concentrations of 3 and 20 µg/mL are considered. Again, the application of the final PopPK model is supporting this discussion.

In conclusion the discussion points regarding the PopPK model for ipilimumab in the advanced melanoma patient population are all supported by the models and by the model evaluations and application performed.

Explicit discussion points for the ER-OS model have been:

- The relationship between ipilimumab C_{minss} and OS hazard ratio was found to be significant. C_{minss} was selected as the summary measure of ipilimumab exposure for this analysis and was based on mechanistic rationale and previous report.
- LDH, Eastern Cooperative Oncology Group (ECOG) status and metastatic status were identified as significant predictors of overall survival (OS).

The final ER-OS model showed a lower OS hazard ratio in patients with higher C_{minss} values. It is appropriate to conclude that survival of previously untreated advanced melanoma patients increased with increasing ipilimumab C_{minss} over the range of exposures achieved with the 10 mg/kg dose, based on the final ER-OS model and the model evaluation and application reported here.

Additionally, elevated LDH, reduced ECOG status and more advanced metastatic status increased the risk of death in patients. Metastatic stage at study entry, abnormal LDH, and poor ECOG performance status are known prognostic factors for poorer survival from metastatic melanoma and could be confirmed here. The influence of gender on OS was inconclusive from this study.

The relationship between ipilimumab exposure and OS seems to be well characterised by the model in the advanced melanoma patient population studied and supported by model evaluations performed.

Explicit discussion points for the ER-iAR model have been:

- Log-odds of immune related irAEs increase with increasing C_{minss} according to an maximum effect (E_{max}) pharmacodynamic model
- Dacarbazine had a marked effect on irAEs, therefore it was included in the base model
- Ipilimumab potency for inducing irAE is generally similar for gastrointestinal and skin and any irAE and the probability of having these irAEs is near maximal for C_{minss} values greater than the median of the 10 mg/kg dose
- Prior anticancer therapy was an important covariate on the probability of irAE occurrences

The final ER-iAR model supported an E_{max} pharmacodynamic model to describe the relationship between increasing immune-related irAEs with increasing C_{minss} values. This is an extension to a previous pharmacometric analysis, supported by more data and a broader C_{minss} values in this study. The model was built according to standard practice and was evaluated extensively consequently this conclusion seems appropriate. Also the a priori inclusion of dacarbazine co-administration was appropriate. Co- administration of dacarbazine with ipilimumab increased the incidence of hepatobiliary immune-related

adverse events but lowered the incidence of gastrointestinal irAEs. Model based estimates of the odds ratios were approximately 9-fold and 0.5-fold, respectively.

The probability of gastrointestinal and skin irAEs was near maximal for C_{minss} values greater than the median of the 10 mg/kg dose, whereas the probability of hepatobiliary irAEs increased over most of the C_{minss} value range produced by 10 mg/kg. The potency of ipilimumab to cause irAE differs by target organ, however the probability of having mild or more severe irAEs differs little. Prior anticancer therapy reduced the risk of any irAE, particularly gastrointestinal and hepatobiliary irAE, however the underlying physiological reasons seem still unknown. The results from the ER-irAE model show an increasing odds ratio for irAEs with increasing C_{minss}, which provides strong support for a role of ipilimumab in the frequency and severity of irAEs.

The relationship between ipilimumab exposure and irAEs seems to be well characterised by the models in the advanced melanoma patient population studied and supported by model evaluations performed.

Clinical evaluator's conclusions on pharmacodynamics

New PD data using the 10 mg/kg posology confirms previous observations regarding increases in ALC with repeated ipilimumab doses over time. Overall, no new data addressing the current application for the 3 mg/kg posology is presented.

Pharmaceutical Sub Committee (PSC) recommendation

From the PSC minutes of 26 May 2014 The PSC resolved to recommend to the Advisory Committee on Prescription Medicines (ACPM) and the TGA that:

It was noted that 11% of samples were excluded due to "pre-dose samples". This is not defined clearly in the Table 3.3.1.5B (not in this AusPAR). More to the point, the "pre-dose samples" are separate to the listing of "Day 1 pre-dose samples". The PSC could appreciate excluding Day 1 pre-dose samples. However, once dosing has commenced the PSC found it hard to justify excluding any pre-dose sample. Importantly, "pre-dose samples" are referred to throughout the report on days after commencement of therapy.

The PSC advised that this is potentially much more significant than the relatively minor 6% missing samples below limit of quantitation (BLOQ).

The PSC recommended the sponsor should be asked to explain this exclusion in more detail and provide a justification.

Dosage selection for the pivotal studies

No pivotal studies have been submitted with this application. There are no newly submitted studies that address dosage selection.

Comments regarding the dosage selection for the current application

The sponsor writes in the 'Summary of Clinical Efficacy';

'Ipilimumab monotherapy (3 mg/kg every 3 weeks for 4 doses) was approved in the US and several other countries for the treatment of metastatic melanoma regardless of prior therapy. In the EU, Australia, and other countries, ipilimumab was approved for the use in previously treated metastatic melanoma. These approvals were primarily based on the OS benefit observed in MDX010-20 (Phase III study of 3 mg/kg ipilimumab ± gp100 versus gp100 alone in pre-treated advanced melanoma), as well as key results from a second

randomised Phase III trial demonstrating OS benefit with ipilimumab in previously untreated advanced melanoma (CA184024; 10 mg/kg ipilimumab + DTIC versus DTIC alone).

This submission presents evidence to support extension of the 3 mg/kg posology to include patients with untreated advanced melanoma based on:

- *Pharmacologic data showing consistent baseline immune status and T cell response in untreated and previously treated subjects*
- *Consistency in PK data between untreated and previously treated subjects*
- *Consistency in efficacy of 3 mg/kg regardless of number or type of prior therapy in MDX010-20*
- *ER data corroborating that the efficacy of ipilimumab is independent of prior therapy*
- *Data from pooled Phase II studies of ipilimumab 3 mg/kg in untreated subjects that demonstrates consistency in safety and efficacy with that in previously treated subjects*
- *Results from the Phase III study of ipilimumab 10 mg/kg plus DTIC versus DTIC confirming clinically meaningful improvement in OS and long term benefit in untreated subjects treated with ipilimumab.*

The durable survival and favourable risk/benefit ratio of ipilimumab in 2 Phase III trials support an update to the therapeutic indication in the ipilimumab Summary of Product Characteristics (SmPC) to include previously untreated, advanced melanoma. Both 3 mg/kg ipilimumab and 10 mg/kg ipilimumab + DTIC provide positive risk/benefit with similar median and long term OS. BMS (the sponsor) recommends the posology of 3 mg/kg ipilimumab for previously untreated advanced melanoma based on a number of considerations outlined in the Clinical Overview.'

Firstly regarding these points listed;

- Randomised evidence in support of the standardisation of therapy has not been provided with the current application
- Data regarding baseline immune status being similar between untreated and previously treated patients is based on the Phase II Study CA184007 which uses the 10 mg/kg posology and maintenance phase. The external validity of this statement for the current application is limited
- Data regarding T cell response at the 3 mg/kg dose was studied in previously treated or untreated subjects in the Phase II CA184004 trial, which included maximally 14 previously untreated patients administered ipilimumab 3 mg/kg monotherapy and included maintenance phase. Whilst this statement is relevant for the current application, the numbers generating this data is small and it is unclear how many of the 14 patients received maintenance therapy
- The pharmacological data within the current application included small numbers of patients relevant to the proposed indication. There were only 14 previously untreated patients who administered ipilimumab 3 mg/kg monotherapy who were included within the analyses of reference. It is unclear how many of the 14 patients received maintenance therapy
- The third point can also be used as support for the use of ipilimumab in the second line setting (for previously treated patients)
- The ER-OS data referred to that was provided within the newly submitted PopPK analysis was based on previously untreated patients from CA184024 (10 mg/kg + DTIC), such that it was not informative for the covariate of previous treatment. If this statement is in reference to the previous ER-OS modelling performed for the previous

evaluation, with reference to the data provided, there were maximally 35 patients included that are relevant to the current application

- Pooled data from Phase II studies, were again based on small numbers of patients relevant to the current application (n = 35)
- The external validity of a study using a 10 mg/kg posology, and its combination with DTIC, is limited for the current application.

Within the 'Clinical Overview', the sponsor writes;

'Extension of the current ipilimumab indication to include patients with advanced melanoma, regardless of prior therapy, is warranted based on 2 randomised Phase III trials of ipilimumab in advanced melanoma demonstrating durable OS benefit. Of all the other therapies for previously untreated advanced melanoma, including vemurafenib, DTIC, and Fotemustine, only ipilimumab has demonstrated a durable OS benefit through at least 2 years. In 2012, the two most widely used oncology guidelines, European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCC), recommended ipilimumab for advanced melanoma, regardless of line of therapy.

While ipilimumab provides a favourable benefit: risk for untreated patients with advanced melanoma both as a 3 mg/kg monotherapy regimen and at a dose of 10 mg/kg plus DTIC, BMS recommends a 3 mg/kg monotherapy based on the following considerations:

- *The efficacy, PK, and PD effects as well as the safety and tolerability of 3 mg/kg ipilimumab are independent of prior therapy*
- *The safety and tolerability of 3 mg/kg ipilimumab monotherapy appears to compare favourably to 10 mg/kg ipilimumab + DTIC, allowing more subjects to receive, on average, the full 4 doses of initial treatment and avoid the additional toxicity from DTIC*
- *New real world OS and safety data from treatment naive patients who received 3 mg/kg*
- *Ipilimumab in the US as their first line of therapy provides confidence in this regimen for advanced melanoma.*
- *3 mg/kg dose is already approved and widely used for previously treated melanoma.*

Extension of 3 mg/kg monotherapy would standardise the ipilimumab safety profile and treatment regimen for advanced melanoma.'

Regarding these points listed by the sponsor;

- Randomised evidence in support of the standardisation of therapy has not been provided with the current application
- Ipilimumab is the only therapy currently for patients with advanced melanoma that provides a durable overall survival. However, the MDX010-20 study trial design included co-administration with gp100 and maintenance therapy and the subgroup analyses have not been prospectively validated. No randomised data has been presented in support of this statement
- Given that the benefits of ipilimumab 3 mg/kg are independent of prior therapy, this can also be interpreted as support for its use (efficacy) in the second line setting
- Direct head to head comparison of the benefits of 3 mg/kg versus 10 mg/kg ipilimumab has not been performed. Cross study comparisons of heterogeneous studies are a poor statistical method of comparing efficacy and have limited external validity for the current application
- Observational interim studies with 'real world data' do not provide high quality level evidence according to conventional grading criteria given the uncontrolled data

collection. One of these interim CSRs did not capture safety events. However, data addressing the pre-submission meeting queries should be reviewed.

Overall, the external validity of the data provided is limited; the number of patients relevant to the current application is small, and in general, data does not directly address the proposed usage. There is a clear lack of randomised data.

To further demonstrate the limitations of cross study comparisons, within this current application the summary of clinical safety refers to the CA184022 where the controlled comparison between the 3 mg/kg and 10 mg/kg dose has been made. Significantly, differences in best overall response rate (BORR), OS and irAEs are observed between posology. This suggests that though numbers in cross study comparisons appear similar, when examined in a controlled setting, significant differences can be observed between different treatments.

'Ipilimumab 10 mg/kg monotherapy was initially studied in Phase II studies. In the dose ranging Study CA184022, a statistically significant trend (p = 0.0015) for increased BORR with increased dose was observed, suggesting a dose effect for ipilimumab activity. A numerical improvement in median OS and 1 year survival rate at 10 mg/kg compared with 3 and 0.3 mg/kg was observed. In addition, a numerical increase in irAEs (any grade) with increasing ipilimumab dose was observed; 0.3 mg/kg (26.4%), 3 mg/kg (64.8%), and 10 mg/kg (70.4%). The overall irAE profile was similar between the 3 and 10 mg/kg treatment groups except for the incidence of Grade 3 to 4 irAEs, which was higher in the 10 mg/kg group than in the 3 mg/kg group (25.4% versus 7.0%).'

Similarly, when CA184024 was compared with ipilimumab 3 mg/kg monotherapy in previously treated melanoma patients (MDX010-20), differences between the frequency and type of AEs can be observed with the different posology and treatment combinations. Thus, though similarities between studies exist, significant anticipated differences also can also be observed within them.

'In CA184024, ipilimumab 10 mg/kg + DTIC demonstrated a clinically and statistically significant increase in OS relative to the global standard of care, DTIC, in previously untreated, advanced melanoma. In this trial, the safety of ipilimumab + DTIC was comparable to that observed for ipilimumab 3 mg/kg monotherapy in previously treated melanoma except for

1. *the occurrence of common DTIC-associated toxicity (for example, nausea, vomiting and myelo-suppression) and*
2. *a higher incidence and severity of hepatitis.*

However, the higher incidence of hepatitis was likely due to the combination of DTIC with 10 mg/kg ipilimumab, since it was higher than expected from DTIC alone or 10 mg/kg ipilimumab monotherapy. In CA184024, there were no treatment-related deaths or GI perforations in the ipilimumab + DTIC group.'

These differences demonstrate the limitations of cross study comparisons. CA184022 illustrates that the efficacy and safety of different treatment schedules is likely to exist, thus studies utilising the 10 mg/kg dosing supply limited support for the current application. CA184024 demonstrates that combination therapy confers anticipated increased toxicity compared to monotherapy, thus studies that do not utilise ipilimumab monotherapy supply limited support for the current application.

In the previous evaluation, the sponsor did not perform an integrated (safety) analysis due to the heterogeneous nature of the studies and populations. The studies in reference overlap those presented in pooled analyses for the current submission. The following excerpt is taken from the previous TGA clinical evaluation report;

'*The safety evidence presented comprises*

- *Routine safety data from the clinical Studies MDXCTLA4-01, MDXCTLA4-02, MDX010-15, CA184004, CA184007, CA184008, CA184022, MDX010-20, MDX010-08*
- *Routine safety data from the ancillary studies (CA184042, MDX010-19, MDX010-13, MDX010-05, MDXCTLA4-04, MDX010-03, MDX010-07, MDX010-17, MDX010-21, MDX010-12, MDX010-11, MDX010-23 and MDX010-24*). In general, for studies in this group, the sponsor states*: 'No analyses were performed on an integrated level for these studies as they represented various tumour types and Ipilimumab doses, schedules, and regimens, including in combination with other therapies.'*

Thus, the bridging data presented needs to be regarded with caution.

In conclusion, with respect to the dosage selection of the sponsor, on the basis of limited data provided relevant to the population of interest (n = 15 to 35), limited external validity of the studies submitted, and the absence of randomised data, there is insufficient evidence to support this application.

Efficacy – overall survival

This section is an evaluation of the efficacy with regard of overall survival benefit.

Studies providing efficacy data

Pivotal efficacy studies

There are no pivotal studies submitted that provide efficacy data for the proposed indication (3 mg/kg monotherapy in the previously untreated population).

Other efficacy studies

There were no studies included in the dossier that investigated the treatment schedule of the proposed usage in the appropriate population for the current application. The majority of efficacy data submitted by the sponsor is deficient with limited external validity due to;

- the use of the 10 mg/kg dosing schedule
- administration of ipilimumab concurrently with other therapy
- the use of a maintenance phase, and
- the investigation of a population of patients not relevant to the proposed usage.

Other efficacy data submitted is based on subgroup analyses which are exploratory and require confirmation in a randomised controlled trial. In addition, all studies including the previously submitted Study MDX010-20, for which the current approved indication is based, included a maintenance phase which limits the external validity of the efficacy data for the current application. In addition, MDX010-20 trial design involved co-administration of ipilimumab with gp100.

The main study contributing efficacy data is one single Phase III Study, CA184024, which uses ipilimumab 10 mg/kg administered concurrently with DTIC, and includes a maintenance phase. According to the statistical principles of clinical trials, CA184024 has limited external validity. The next subsection provides more data addressing the current application from pooled analyses.

Other studies reviewed within this section that have been submitted in support of the current application include one Phase II study interim report for CA184042 which uses a 10 mg/kg dosing, a Phase I study with a secondary endpoint of efficacy (CA184078), two interim reports for observational Studies (CA184332, CA184338), and a report for the

extended access program (EAP) for which efficacy analyses were performed only on patients treated with the 10 mg/kg dosing (CA184045). Efficacy results were not reviewed for MDX010-16 as the study design was for the adjuvant setting and the median time to disease relapse results is immature since less than 50% of the subjects relapsed and the median value was not reached. In addition, this study was terminated early. These studies have been included due to their reference in the pre-submission meeting. These studies contribute limited supportive efficacy data due to the use of the 10 mg/kg dosing, concurrent administration with other drugs, Phase I design, observational design, and an alternate primary endpoint to efficacy.

With reference to the current application, the OS obtained by patients treated by previous conventional systemic therapy for this setting should be noted. It also should be noted that there are some long term survivors observed in the standard (non ipilimumab) treatment arms. Trials in previously untreated advanced melanoma patients demonstrate a median OS of approximately 9 months and estimated 1 year OS rate of approximately 36% as historical benchmark for DTIC monotherapy. Fotemustine, the only other chemotherapy used as standard treatment, has a median OS of 7.2 months and estimated 1 year OS rate of approximately 30%.[2],[3],[4],[5]

For the evaluation of the studies please see Attachment 2.

Evaluator's conclusions on efficacy for overall survival

There was no investigation of efficacy utilising ipilimumab 3 mg/kg monotherapy according to the proposed usage where efficacy was the primary endpoint. Current claim utilises the concept of non-inferiority but appropriate studies have not been carried out prospectively to test this.

A single Phase III Study (CA184024) demonstrates a statistically significant survival benefit obtained for previously untreated patients with advanced melanoma administered combination ipilimumab 10 mg/kg and DTIC versus DTIC monotherapy. The study design, study execution, quality of the efficacy data, and plausibility of hypothesis tested were robust.

However, this study has been submitted by the sponsor as part of the 'bridging argument' for the proposed usage. The current application seeks to use the 3 mg/kg dosing schedule and seeks use of ipilimumab as monotherapy. In comparison, this Phase III study utilises a different posology, utilises drug administration concurrently with DTIC and incorporated a maintenance phase of treatment. Thus, this study has limited external validity for the current application. It therefore provides limited relevant evidence for the proposed usage.

An interim report from one Phase II Study (CA184042) was submitted which used 10 mg/kg ipilimumab in previously untreated patients with brain metastases without (Arm A; n = 51) or with concomitant steroids (Arm B; n = 21). This study provides supportive evidence for the global disease control rate and survival benefit with use of ipilimumab 10 mg/kg in patients with metastatic melanoma with brain lesions, of which patients without concomitant steroids have an improved outcome compared to patients on steroids.

[2] M.F. Avril, Fotemustine Compared With Dacarbazine in Patients With Disseminated Malignant Melanoma: A Phase III Study *J Clin Oncol* 2004;22: 1118-1125
[3] Chapman et. al Phase III Multicenter Randomised Trial of the Dartmouth Regimen Versus Dacarbazine in Patients With Metastatic Melanoma *J Clin Oncol* 1999; 17; 2745-2751
[4] Middleton et al Randomised Phase III Study of Temozolomide Versus Dacarbazine in the Treatment of Patients With Advanced Metastatic Malignant Melanoma *J Clin Oncol* 2000; 18 :158-166
[5] Patel et al, Extended schedule, escalated dose temozolomide versus dacarbazine in stage IV melanoma: Final results of a randomised phase III study (EORTC 18032) *Eur J Cancer* 2011;47: 1476-1483

This study is submitted by the sponsor as part of the 'bridging argument' for the proposed usage. The external validity of this study is limited in the context of the current application. Limited supportive evidence is provided by this data as a 'bridging argument' given the use of the 10 mg/kg posology. The population examined in this study differs to MDX010-20 and other studies which utilise the 3 mg/kg posology, limiting the external validity of comparisons. The study was not randomised. It therefore provides limited relevant evidence for the proposed usage.

Pooled analyses using previously evaluated and newly submitted studies demonstrated numerically similar OS rates, despite use of 3 mg/kg dosing, 10 mg/kg dosing, and monotherapy or combination treatment schedules. The populations between studies appear similar. However, uncontrolled, post hoc exploratory, non-confirmatory cross study comparisons do not provide sufficient quality evidence for robust conclusions, and are only useful for hypothesis generation. There is limited external validity of the comparison of survival rates between different treatment schedules and patient populations. The inclusion of bias, in particular selection bias and the use of concomitant therapy, is not accounted for. The pooled analyses provided efficacy data for (maximally) 35 previously untreated patients who were administered 3 mg/kg ipilimumab monotherapy. The additional benefit of pooled data from two studies is limited, when the numbers in each study are small (n = 20 + n = 15). ER-OS modelling from the new PopPK report has limited external validity for the current application due to its use of patients' data only from CA184024. PopPK modelling from the previous submission included a small number of patients relevant to the current application (maximally n = 35). Furthermore, all studies included a maintenance therapy phase.

Thus, with respect to the current application for use of ipilimumab 3 mg/kg monotherapy in previously untreated patients, the relevant data provided by the pooled analyses derived from heterogeneous studies is considered limited, and does not provide sufficient quality of evidence for regulatory purposes.

Other studies summarised within this section (CA184078, two interim reports from observational post-marketing studies, and one interim report summarising data from the EAP) were submitted by the sponsor as additional support for the proposed usage. These studies were shown to demonstrate similar numerical OS rates observed within the controlled studies. However, evidence provided by these studies is considered not to be of sufficient quality for robust conclusions. This is due to Phase I study having limited relevance to the proposed usage (study design, primary endpoint, numbers investigated, 10 mg/kg posology), and the low quality level of evidence contributed by uncontrolled data collection in the three observational studies. Data was also immature. Thus, the Phase I study provides limited quality evidence and limited relevant evidence for the proposed usage (limited external validity). The observational studies provide limited quality evidence for the current application.

Overall, limited data is presented that is relevant to the current application which seeks approval for the use of ipilimumab 3 mg/kg monotherapy in previously untreated patients. No randomised data addressing the proposed usage was provided.

Data derived pooled from maximally 35 patients across two Phase II studies provides insufficient evidence for robust conclusions on the efficacy of the drug for the proposed usage. It is impossible to derive an understanding of the efficacy of the drug for the proposed usage from studies that utilise a different dosing schedule (10 mg/kg) or treatment schedule (combination therapy and maintenance therapy). Though pooled data has been presented as a 'bridging argument' to indirectly address the efficacy of ipilimumab 3 mg/kg monotherapy in previously untreated patients, the limited numbers of relevant patients within pooled analyses and the use of cross study comparisons argues strongly that there is insufficient evidence available to support the current application. The 'bridging argument' has not been established on randomised data. The 'bridging

argument' has been established on cross study comparisons and pooled data from heterogeneous studies. Thus the likelihood of bias (for example selection bias, concomitant use of other therapy), within these analyses needs to be considered as unaccounted for given the uncontrolled, non-randomised methodology utilised. The data presented in support of the current application does not meet the statistical principles of clinical trials guidelines.

Whilst note is made of the clinical need for effective therapy in this patient population, the likely biological plausibility for the efficacy of the proposed usage, the long term survival benefit provided for a subgroup of previously treated patients, the desire to avoid toxicity with higher dosing schedules, and the pre-submission meeting notes, on the presented data alone insufficient evidence has been provided that directly addresses or supports the current application.

Therefore, the efficacy of the proposed usage (or the optimal dose) in the untreated population has not been sufficiently proven due to the absence of randomised data and absence of data with sufficient quality or relevance.

Efficacy for OS with BRAFV600E mutation positive tumours

This section discusses efficacy for overall survival benefit in patients with BRAFV600E mutation positive tumours.

A retrospective analysis of the BRAF mutation status of patient tumours obtained in the Phase II Study CA184004 was performed. This previously evaluated study was a randomised, double blind, multicentre study of 82 pre-treated or untreated subjects with un-resectable Stage III or Stage IV melanoma. Subjects received ipilimumab 3 mg/kg (n = 40) or 10 mg/kg (n = 42) every 3 weeks for 4 doses followed by maintenance dosing in eligible subjects. The BRAFV600E mutation status was assessed in 80 tumour biopsies by two competitive allele specific polymerase chain reaction (PCR) based assays. Of these samples, data on disease control were available for 69 subjects.

Rates of objective responses (CR or PR) and SD in subjects with BRAFV600E mutation positive tumours (0% CR, 10% PR, and 20% SD) were comparable to those in subjects with the wild type BRAF (3.2%, CR, 9.7% PR, and 22.6% SD). Eleven subjects had durable disease control of which 6 (55%) had BRAFV600E mutation positive tumours and 5 (45%) did not. In the 48 subjects without durable disease control, the mutation frequency was 50%. Therefore, in this study of 80 tumours, the sponsor concludes that ipilimumab was shown to be equally active in BRAFV600E mutant and wild type melanoma.

No information was provided by the sponsor of the frequency of BRAFV600E status stratified according to previous treatment status, study treatment dose, response and survival (combined).

For further details of the evaluation please see Attachment 2.

Evaluator's conclusions on use in patients according to BRAF mutation status

Limited evidence is provided regarding the efficacy of ipilimumab regardless of BRAFV600E mutation status, from a small retrospective study of 82 patients without specific details of treatment or survival provided.

Regardless of this, data from a single retrospective Phase II study of 82 patients is not considered sufficient evidence to support use of ipilimumab as first line therapy regardless of BRAFmt status for regulatory purposes. Other relevant BRAF mutations (for example BRAFV600K or BRAFV600D) were not detected in this single study, likely due to insufficient numbers to detect less frequent mutations (the power of the study was limited). Numbers examined were small overall, and of particular interest, the total

number of patients with a tumour response to the drug was smaller. Comprehensive information was not provided by the sponsor with treatment and clinical outcome stratified according to mutation status. Thus, response to ipilimumab according to mutation status is insufficiently characterised. Therefore, there is insufficient evidence to support the conclusion written by the sponsor that '*Therefore, ipilimumab is equally active in BRAF mutant and wild type melanoma.*'

From a 'real world' oncological perspective, patients with mutation positive tumours are unlikely to receive non targeted therapy (for example chemotherapy, immunotherapy) prior to targeted therapy in order to maximise the number of clinical treatment lines available. The setting whereby therapy is used as first line treatment is usually established by the appropriate randomised controlled trial demonstrating efficacy (superiority) in relevant populations of sufficient size.

The sponsor has proposed a change to the PI, to alter clinical trial information for the study description of MDX010-20 was updated to include the following statement: 'Patients were enrolled regardless of their baseline BRAF mutation status.' Whilst this statement is true with respect to the trial, this may be mistaken to imply that the efficacy of ipilimumab has been sufficiently examined and proven to be equal in BRAFmt positive and negative tumours. The efficacy of ipilimumab according to BRAF mutations status has been sufficiently investigated, and the proposed change to the PI is not supported with adequate data to justify this change. A trial to directly compare the efficacy of BRAF targeted therapy versus ipilimumab in the first line setting with BRAFmt status prospectively collected, would need to be performed to provide randomised evidence for the benefit of ipilimumab in the first line setting.

Safety

Studies providing safety data

For the evaluation of the studies providing safety data please see Attachment 2.

Patient exposure

Note should be made of the proposed usage being for ipilimumab 3 mg/kg monotherapy and the external validity (relevance of the evidence) of the majority of listed studies in Table 6 and Table 7.

Table 6: Exposure to ipilimumab and comparators by patient numbers in clinical studies

Study type/ Indication	Controlled studies			Uncontrolled studies	Total Ipilimumab
	Ipilimumab	Ipilimumab with Carboplatin/Paclitaxel	Ipilimumab with DTIC	Ipilimumab	
Clinical pharmacology	20	20	19	-	59
Ipilimumab 3 mg/kg					
Monotherapy +peptide	- 25	- -	- -	120 -	145 -
Subtotal	25			120	145

Study type/ Indication	Controlled studies			Uncontrolled studies	Total Ipilimumab
Indication 1					
Ipilimumab 10mg/kg					
+DTIC Monotherapy Plus peptide +steroids	- 26 25 72		247 - - -	- 830 - -	247 856 25 72
Subtotal Indication 2	123		247	830	1200
TOTAL	168	20	266	950	1404

Table7: Patient exposure to ipilimumab in clinical studies according to dose and duration

Study type/ indication	Induction	Maintenance		
	≥ 3 mo.	≥ 6 mo.	≥ 12 mo.	Any duration
Clinical pharmacology	59	0	0	59
Ipilimumab 3 mg/kg				
Monotherapy+peptide	25	0	-	25
Active-controlled				
Uncontrolled	120	-	-	120
Subtotal Indication 1	145	-	-	145
Ipilimumab 10mg/kg				
With DTIC	247	43	-	247
Monotherapy versus. with steroids	72	13	-	72
Monotherapy With peptide Uncontrolled	26 25 830	6 6	- -	26 25 830
Subtotal Indication 2	1200	68	-	1200
TOTAL	1404	68	-	1404

Note should be made that analysis was limited to the induction (3month) period only for some studies.

Evaluator's conclusions on safety

There were no pivotal trials submitted relevant to the proposed usage.

From data pooled from previously evaluated Phase II studies, maximally 35 patients investigated may provide relevant safety data. However, from the sponsor's presentation of data, safety information relevant to the population indicated in the proposed usage was not clear. The sponsor was requested to address this.

Of the trials that are provided in the dossier, these provided limited relevant evidence for the proposed usage due to differences variously in the dose, regimen, or use in combination with chemotherapy, line of treatment as mentioned already. There are numerous issues regarding the source data and subsequent analyses.

Overall, there are uncertainties regarding the safety data for all these studies regarding;

1. The appropriate documentation of AEs.
2. The grading of AEs.
3. The allocation of causality for AEs.
4. The summarised data is limited due to the two previous points and the text does not comprehensively summarise clinically meaningful information.
5. The presentation of data appears to minimise the frequency of clinically meaningful safety data, through the use of MedDRA preferred terms which are highly specific (in comparison to considering higher level terms, collapsing terms or summarising the data in a clinically meaningful way).

As a result, evaluation of the safety of the drug within these trials was not possible.

Of pertinence, an EORTC Phase III trial recently presented at the annual American Society of Clinical Oncology investigating the benefit of adjuvant Ipilimumab 10 mg/kg monotherapy in healthy patients with resected Stage III melanoma raises significant clinical concerns regarding the safety of the proposed usage. Of this healthy population investigated, within the study arm, five study related deaths were observed, six study related GI perforations were observed and the rate of immune mediated adverse reactions (imARs) were generally numerically higher than those presented in the reports submitted within the dossier.

In conclusion, due to the lack of randomised evidence relevant to the proposed usage and the uncertainties regarding the safety data of the submitted 'bridging' studies, the sponsor has not adequately demonstrated the safety of the drug for the application. A recent report raises significant clinical safety concerns for use of the drug in a healthy population.

First round benefit-risk assessment

First round assessment of benefits

The benefits of Ipilimumab 3 mg/kg monotherapy in untreated patients with advanced melanoma include:

- The evidence for efficacy for overall survival benefit at this dose in previously treated patients, as demonstrated in the previously evaluated study, MDX010-20. Some patients derive a durable long term survival benefit. However, with reference to the statistical principles of clinical trials guidelines, consideration should be made regarding the external validity of this study for the current application which seeks use in previously untreated patients and use as monotherapy without consideration of co-administration of gp100 or a maintenance phase.
- The unmet need remains for effective treatment options with durable efficacy for this patient group.

First round assessment of risks

The risks of the proposed usage could not be effectively evaluated due to:

- The limited evidence provided addressing the proposed usage in the relevant population
  - There is an absence of randomised data relevant to the population of interest for the current application
  - The number of patients included within this submission that are relevant to the current application varies between n = 15 to n = 35.

The sponsor is requested to provide safety data for the previously untreated patients who were treated at the proposed dose for evaluation (see questions for sponsor). Please note that the safety analysis for Study CA184024, while not directly relevant in establishing safety for the proposed usage as monotherapy at 3 mg/kg dose, could not be completed with the data presented by the sponsor. The sponsor is requested to address the issues raised in the questions to the sponsor). Please also note the significant safety issues highlighted (in Section 8.11- relevant new data not submitted by the sponsor- of Attachment 2).

First round assessment of benefit-risk balance

A benefit-risk balance is not currently able to be completed due to the aforementioned issues.

First round recommendation regarding authorisation

No pivotal efficacy or safety data are suppled in support for the proposed indication. Of primary significance;

- Safety data provided for studies submitted with this application did not adequately demonstrate safety
- New data raises concern regarding the safety of the proposed usage.

Secondarily, the data provided relevant to the population of interest for the current application insufficiently addresses the statistical principles for clinical trials guidelines due to the following reasons;

- Post hoc pooled efficacy data from heterogeneous studies maximally incorporated maximally 35 patients investigated in Phase II studies that are relevant to the current application. Subgroup analyses were not planned and have not been prospectively validated. (Insufficient 'study' size to address the proposed usage and limited external validity).
- Pooled pharmacological data from heterogeneous studies incorporated only 14 previously untreated patients administered ipilimumab 3 mg/kg monotherapy relevant to the current application.
- The external validity of data from trials utilising a different posology to the current application is limited.
- The external validity of data from trials utilising combination therapy is limited in the context of the current application for monotherapy.
- The external validity of data from trials utilising a maintenance phase is limited in the context of the current application for monotherapy.
- The external validity of data from trials investigating patient populations that differ to the current application is limited.
- There was no randomised data presented relevant to the population of interest or the treatment schedule of interest.

As a result, the safety and the efficacy of the proposed usage have not been adequately demonstrated by the sponsor. The clinical evaluator's recommendation is that the application is not authorised.

The clinical evaluator also raised issues with regard to the PI and CMI but these are beyond the scope of the AusPAR.

Clinical questions

Pharmacokinetics

With reference to the PopPK analysis:

1. Could the sponsor please explain their rationale for only examining ER-OS response with the dataset from CA184024, when the previous report included other studies?
2. Table 3.3.1.5B annotating samples included in the dataset, not is made that approximately one third of samples (1188 out of 4388) were excluded if below the limit of quantification, if quantifiable concentrations were detected pre-dose (not described further) or due to the mismatching of samples (not described further). Furthermore it is noted that this includes 11% samples were excluded due to 'pre-dose samples' separate to the listing of 'Day 1 pre-dose samples'. Could the sponsor please clarify each category? For example, how many, and how high were the ipilimumab levels detected pre-dosing? Why was a level detected prior to dosing? Can the sponsor please explain and justify the exclusion of samples once dosing has commenced 'Day 1 pre-dose samples'?
3. For the covariate analysis, the number of covariates examined is smaller than those described. These omitted variables include baseline BSA, ideal body weight, albumen, and race. Can the sponsor please provide explanation for the omission of covariates?
4. With the generation of the base PK model (5.1.1.1) 'There were some subjects who were had aberrant concentrations, and the inclusion of those concentrations' prevented successful analysis ('termination'?) of NONMEM and thus these samples were excluded. This is in addition to the 6 excluded samples described in the same paragraph. Could the sponsor please provide more information on the 'aberrant' samples; how many were there? Why were these considered aberrant (assay issue versus outliers)?

Pharmacodynamics

No questions.

Efficacy

5. For the pooled efficacy analysis, Table 7-5 and the sponsor's text are unclear regarding the total number of patients relevant to the proposed indication from MDX010-08. The study summary in Table 7-5 and text refer to these patients as previously treated. However, these patients are included under the pooled total number of previously untreated patients.

   Of the total 35 patients indicated;

   Can the sponsor please clarify how many patients from MDX010-08 were previously untreated (versus chemotherapy naïve as indicated in the table and text)?

   Can the sponsor clarify how many randomised patients received 3 mg/kg Ipilimumab monotherapy without any maintenance therapy?

Of this subsequent total of patients clarified by the previous questions, can the sponsor please provide the interquartile range of median follow-up, and clarify the OS survival rates obtained for this group relevant to the proposed indication?

6. For the pooled efficacy analysis, Table 7-8, indicates that within the pooled previously untreated group there is a patient who was followed up for only 4.8 days, and in the pooled chemotherapy naïve group a patient followed up for 0.9 days. Can the sponsor please provide details of the patients' performance status, the reasons for the short duration of follow-up and confirmation that these patients met the eligibility criteria of the relevant study? Can the sponsor please provide the interquartile ranges for the median follow-up relevant to the table?
7. Given the uncertainty of the differences in efficacy and safety issues between the 3 mg/kg and 10mg/kg dosing schedule in previously untreated and previously treated patients, the sponsor is requested to provide an interim summary of efficacy data for CA184169.

Safety

Queries regarding safety data relevant to the proposed usage

There were maximally 35 patients from pooled Phase II studies previously submitted that provide safety data relevant for the proposed usage.

8. For the pooled safety data, as outlined in the questions to the sponsor regarding efficacy (above), it is unclear how many patients presented within the pooled analyses are relevant to the proposed usage. Of the patients clarified by the first question, can the sponsor provide the relevant safety data for these patients? The sponsor is requested to represent in text and table the summary of all information as presented within the pooled safety analyses (from the Clinical Overview and Summary of Clinical Safety). In doing this, the following requests are made to permit evaluation:
    a. Source data should be checked to ensure AEs are captured, grading is appropriate and allocation of causality is accurate. To facilitate review by the evaluator, please provide amendments of previously submitted data in a tracked copy and cleaned/untracked copy.
    b. Safety data should be clearly presented and defined in a clinically meaningful way to avoid the underrepresentation of data. Higher clinical terms should be collapsed in a meaningful way with each preferred term listed below. The method of analysis and collation of synonymous clinically relevant terms should be defined.

In addition, the sponsor should summarise for these patients the number of episodes for all grades of AEs and imARs that required hospitalisation for investigation or management, the use of any systemic corticosteroid, infliximab use, other immunosuppressant use, surgical intervention, total parenteral nutrition (TPN) or any other relevant medical intervention. Please summarise with sufficient detail included for each subcategory.

9. Given the uncertainty of the differences in safety issues between the 3 mg/kg and 10mg/kg dosing schedule in previously untreated and previously treated patients, the sponsor is requested to provide an interim summary of safety data for CA184169.

General queries regarding source data from studies evaluated that provide limited evidence for the proposed usage

The sponsor has not provided safety data in a clinically meaningful manner that allowed the satisfactory assessment of the safety data for the studies submitted with this application. These issues have been discussed.

a. When narratives of SAEs within the dossier have been reviewed, it appears that AEs described within the narrative are not consistently captured in the listings of AEs and imARs found at the beginning of the narrative. This includes both the grading of AEs and the event itself.

b. Can the sponsor please clarify if these lists for AEs and imARs should comprehensively include what is described within the narrative? Are these the data sources that are used to generate summary tables and analyses? The inconsistency between these summary lists and the narrative has been observed for all submitted trials with narratives available.

   Examples are given in Section 8 according to study and are also summarised (Please see Attachment 2).

   Please can the sponsor clarify if these lists at the beginning of each narrative are intended to capture and grade all events, and these lists are subsequently used for analyses?

c. Can the sponsor please also indicate if Grade 5 events were captured on the SAE narrative, and if not, how were they collated/captured for all CSRs? Specifically, should the summary listing at the top of the narrative, capture a grade 5 event if the patient died? Can the sponsor explain how they ensured that deaths were uniformly and comprehensively captured?

d. Can the sponsor please clarify for the allocation of SAEs versus AEs, who identified these events and how were these events defined (the criteria within the CSR does not explain this)? Was it according to investigator, sponsor, or CRF? Who judged if an event 'may have jeopardised the subject'? What level of 'medical' intervention warranted a SAE?

e. Can the sponsor please provide or indicate where the description of definitions, criteria and the background behind the allocation of imARs, as developed by the sponsor and the FDA can be found?

f. Could the sponsor please clarify or indicate where the definition for a 'severe' versus 'serious' AE is found? For example, in CA184024, Table 8.1 'Summary of Safety – treated subjects', (page 141), this table separately lists severe AEs as Gr 3/4 events, serious AEs, related AEs, AEs leading to drug discontinuation, and death.

g. Can the sponsor please clarify if the document of cumulative line listings of serious events comprehensively captures the SAEs for the studies within the dossier? Does this include deaths? Cross referencing between a CSR and the cumulative line listing for AEs described within the body of the CSR was often not possible. Can the sponsor also indicate where the key for abbreviation in this document is located?

The clinical evaluator also raised questions related to specific safety reports from the clinical studies. As this was extensive the details are included in Attachment 2. Under the following headings

- Specific Questions regarding the data from studies evaluated that provide limited evidence for the proposed usage

- Selected pertinent safety queries raised through the process of evaluation.

Second round evaluation of clinical data submitted in response to questions

For the second round evaluation of clinical data submitted in response to questions please see Attachment 2.

Second round benefit-risk assessment

Second round assessment of benefits

The main benefit of ipilimumab 3 mg/kg in the proposed usage is conferral of an overall survival benefit, relative to dacarbazine. There is a lack of direct evidence for this. There is also a lack of data comparing ipilimumab with more recently approved therapies, for example the BRAF and MEK inhibitors in BRAF V600 mutant disease. There is no information provided about concomitant use with such treatments.

Second round assessment of risks

The main risk of ipilimumab 3 mg/kg in the proposed use is that patients may experience the undoubted toxicities of treatment at an earlier stage of advanced disease.

There is no sign toxicities will be qualitatively different from those observed in second line treatment, but there is no direct and robust evidence to inform users about AE frequencies in the first line setting. A risk is that AE frequencies may be elevated in this setting, relative to experience with ipilimumab as a second line agent.

The key reassurance that toxicities of treatment are worth the risk is the indirect evidence of OS benefit. There is no information provided about impact on quality of life, and one risk is that quality of life may be degraded despite improved OS.

Second round assessment of benefit-risk balance

The benefit-risk balance of ipilimumab 3 mg/kg in patients previously untreated for their advanced melanoma is favourable. Given the indirect evidence for both efficacy and safety, there is considerable uncertainty attached to this assessment. However, the clinical evaluator considers that in the circumstances (that is treatment of a life threatening condition, especially where patients may not have the opportunity to commence a second line agent) the degree of uncertainty is acceptable.

Second round recommendation regarding authorisation

The proposed change is to include use as first line therapy for patients, so that the formal indication for ipilimumab will read:

> *Yervoy/Winglore, as monotherapy, is indicated for the treatment of patients with unresectable or metastatic melanoma.*

The clinical evaluator recommends this change be authorised.

This wording does not refer to induction use or maintenance use, and in theory allows both uses. The PI's Dosage and Administration section countenances induction and re-induction but not maintenance. The clinical evaluator thinks this is a satisfactory approach.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (RMP) Yervoy EU-RMP version 8.2 (data lock point 18 September 2012); Australian-specific Annex (ASA) version 1 dated 29 November 2013 which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown in Table 8.

Table 8: Ongoing safety concerns

Ongoing safety concerns	
Important identified risks	• GI immune related adverse reactions (irARs) (for example diarrhoea, colitis, GI perforation) • Hepatic irARs (for example hepatitis) • Skin irARs (for example rash, pruritis) • Neurologic irARs (for example neuropathy) • Endocrine irARs (for example hypopituitarism, hypothyroidism, adrenal insufficiency) • Other irARs (for example pneumonitis, nephritis, non-infective myocarditis and pancreatitis)
Important potential risks	• Immunogenicity • Difference in efficacy in women ≥ 50 years
Important missing information	• Reproduction and lactation data • Paediatric data • Data in ethnic groups • Potential pharmacodynamic interaction with systemic immunosupressants • Severe hepatic impairment • Severe renal impairment • Safety in patients with autoimmune disease

Pharmacovigilance plan

Table 9 is a summary of the pharmacovigilance activities proposed.

Table 9: summary of proposed pharmacovigilance activities

Important identified risks	Pharmacovigilance
GI irARs	• Routine pharmacovigilance • Additional pharmacovigilance including: targeted questionnaire for GI perforation or colectomy, post-marketing epidemiologic prospective cohort study (ongoing)
Hepatic irARs	• Routine pharmacovigilance • Additional pharmacovigilance including: targeted questionnaire for severe hepatotoxicity, post-marketing epidemiologic prospective cohort study (ongoing)
Skin irARs	• Routine pharmacovigilance • Additional pharmacovigilance including: targeted questionnaire for erythema multiform, Stevens-Johnson Syndrome or toxic epidermal necrolysis, post-marketing epidemiologic prospective cohort study (ongoing)
Neurologic irARs	• Routine pharmacovigilance • Additional pharmacovigilance including: targeted questionnaire for Guillain-Barre syndrome or severe autoimmune neuropathy, post-marketing epidemiologic prospective cohort study (ongoing)
Endocrine irARs	• Routine pharmacovigilance • Additional pharmacovigilance including: post-marketing epidemiologic prospective cohort study (ongoing)
Other irARs	• Routine pharmacovigilance • Additional pharmacovigilance including: post-marketing epidemiologic prospective cohort study (ongoing)
Severe infusion reactions	• Routine pharmacovigilance; • Additional pharmacovigilance including: post-marketing epidemiologic prospective cohort study (ongoing)
Important potential risks	
Immunogenicity	• Routine pharmacovigilance
Difference in efficacy in women ≥ 50 years	• Additional pharmacovigilance including: subpopulation analyses will be conducted in future clinical trials
Missing information	
Reproductive and lactation data	• Routine pharmacovigilance • Additional pharmacovigilance including: completed nonclinical study on embryo-foetal development and pre-and post-natal development study

Important identified risks	Pharmacovigilance
Paediatric data	• Routine pharmacovigilance • Additional pharmacovigilance including: ongoing paediatric study CTEP7458/CA184070;
Data in ethnic groups	• Routine pharmacovigilance
Potential pharmacodynamics interaction with systemic immunosuppressants	• Routine pharmacovigilance
Severe renal impairment	• Routine pharmacovigilance
Severe hepatic impairment	• Routine pharmacovigilance
Safety in patients with autoimmune diseases	• Routine pharmacovigilance
Long-term safety	• Routine pharmacovigilance • Additional pharmacovigilance including: post-marketing epidemiologic prospective cohort study (ongoing)

Risk minimisation activities

The sponsor proposes routine risk minimisation measures through the product information for all the safety concerns. In addition, the sponsor has ongoing Communication Plan to mitigate the risks of immune related adverse reactions. The Communication Plan comprises two parts:

- Healthcare Professional Frequently Asked Questions (FAQ) brochure
- Patient Information Brochure including a detachable alert card.

Reconciliation of issues outlined in the RMP report

Table 10 summarises the first round evaluation of the RMP, the sponsor's responses to issues raised by the RMP evaluator and the evaluation of the sponsor's responses.

Table 10: Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
1. Safety considerations may be raised by the clinical evaluator through the consolidated request for information and/or the Clinical Evaluation Reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the RMP, and any specific	As noted in Table 1.5.2.9 of EU-RMP v8.2, optic neuritis is included as an "other irAR". While irARs with ipilimumab occur predominantly in the GI tract, liver, skin and endocrine organs, irARs can more rarely occur anywhere in the body. These "other irARs" are an identified risk for ipilimumab. Not all of the events that are included in the category of other irARs are discussed individually in the RMP. … There were a total of 35 previously	The sponsor has provided detailed answers to the clinical evaluator's questions in its response. Recommendations regarding these issues are made in the context of post-market RMP as follows: Optic neuritis – as the case of optic neuritis was assessed by the investigators as 'study treatment related', this

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.	untreated patients who received ipilimumab 3 mg/kg monotherapy; whereas, 55 previously untreated patients received any 3 mg/kg ipilimumab containing treatment (including combinations). For discussions in the RMP, data were presented for ipilimumab 3 mg/kg in combination with other drugs, in order to present larger patient numbers and a more conservative safety assessment.	should be added to the ASA as a 'potential risk'; Frequency of adverse events – gastrointestinal, hepatic irAEs and other irAEs have been included in the list of safety concerns in the RMP. The sponsor should undertake to give specific consideration to data analysis and ensure consistent reporting in the periodic safety update reports (PSURs). Specific recommendation on AE reporting is referred to the Delegate.
2. As the TGA has previously evaluated an RMP for ipilimumab (PM-2010-02212-3-4), the focus of this evaluation is on the changes to the RMP that could have an impact on the safety profile and any new safety related information since the last evaluation.	Not applicable	Not applicable
3. The sponsor has provided a list of studies referenced in the EU-RMP that are ongoing in Australia in Section 2.2 of the ASA. The sponsor should also provide the anticipated dates for their submission in Australia.	The study reports will be considered for submission to TGA when the results become available. Estimated completion dates for studies CA184143, CA184029, CA184169, and CA184043 are included in the EU-RMP.	The sponsor's response is acceptable. Significant safety findings from the studies should be reported to the TGA immediately. The study reports can be submitted with future PSURs when they become available.
4. In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft PI be revised to include instructions on dose calculation as follows: 'The prescribed dose for the patient is given in mg/kg. Based on this prescribed dose, calculate the total dose to be given. More than one vial of Yervoy concentrate may be	This text will be added to the product information. In addition to addressing the specific recommendations made in the RMP evaluation report, the sponsor wishes to clarify a statement in the RMP evaluation report regarding the ongoing Communication Plan. Section 10.1 of the RMP evaluation report indicates that the Communication Plan comprises two parts: • Healthcare Professional Frequently Asked Questions (FAQ) brochure • PI Brochure including a	The sponsor's response is acceptable. The recommendation regarding the Australian PI revision remains, awaiting consideration by the Delegate. The RMP evaluator has noted the sponsor's clarification on the additional risk minimisation activities. The sponsor should update the communication tool for healthcare professionals and patients to reflect the

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
needed to give the total dose for the patient. Each 10 ml vial of Yervoy concentrate provides 50 mg of ipilimumab; each 40 ml vial provides 200 mg of ipilimumab. The total ipilimumab dose in mg = the patient's weight in kg x the prescribed dose in mg/kg. The volume of Yervoy concentrate to prepare the dose (ml) = the total dose in mg, divided by 5 (the Yervoy concentrate strength is 5 mg/ml)'	detachable alert card. • These components are those which are implemented in the EU. The specific Communication Plan for Australia is that which is outlined in Table 5.2 of the ASA: • HCP communication tool (Yervoy irAR Management Guide) • Patient communication tool.	proposed extension of indication. The updated version of these documents should be submitted to the TGA for review before the date of the approval.

Summary of recommendations

Issues in relation to the RMP

Recommendation 3: The sponsor's response is acceptable. Significant safety findings from the studies should be reported to the TGA immediately. The study reports can be submitted with future PSURs when they become available.

Recommendation 4: The sponsor's response is acceptable. The recommendation regarding the Australian PI revision remains, awaiting consideration by the Delegate.

The RMP evaluator has noted the sponsor's clarification on the additional risk minimisation activities. The sponsor should update the communication tool for healthcare professionals and patients to reflect the proposed extension of indication. The updated version of these documents should be submitted to the TGA for review before the date of the approval.

Additional recommendations

- Optic neuritis; as the case of optic neuritis was assessed by the investigators as 'study treatment related', this should be added to the ASA as a 'potential risk'.
- Frequency of adverse events; gastrointestinal, hepatic irAEs and other irAEs have been included in the list of safety concerns in the RMP. The sponsor should undertake to give specific consideration to data analysis and ensure consistent reporting in the PSURs. Specific recommendation on AE reporting is referred to the Delegate.

A*dvice from the Advisory Committee on the Safety of Medicines (ACSOM)*

ACSOM advice was not sought for this submission.

Suggested wording for conditions of registration

Implement Yervoy EU-RMP version 8.2 (data lock point 18 September 2012) with Australian-specific Annex version 1 dated 29 November 2013 and any future updates as a condition of registration.

VI. Overall conclusion and risk/benefit assessment

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

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

The clinical dossier focused on the provision of new and collated data supportive of the efficacy of the drug in the treated and untreated population, at both the 3 mg/kg and 10 mg/kg dosing, as combination therapy and as monotherapy, with other additional information in support of proposed changes to the PI.

The clinical evaluator has reviewed the submitted data, which included:

Three completed clinical study reports;

- Phase III CA184024 for efficacy, safety and pharmacokinetic data for ipilimumab 10 mg/kg in combination with dacarbazine (DTIC), with a maintenance phase.
- Phase II CA184042 for efficacy and safety for ipilimumab 10 mg/kg monotherapy (with a maintenance phase) for patients with brain metastases with or without concurrent steroid use.
- Phase I CA184078 pharmacokinetic, pharmacodynamic, safety data and secondary efficacy data of ipilimumab 10 mg/kg monotherapy and as combination therapy (all with a maintenance phase).

Three abbreviated clinical study reports (synopses);

- MDX010-16 provides safety, and early efficacy data for use of ipilimumab in the adjuvant setting in a prematurely terminated study. This study was terminated early following the sponsor's acquisition of Medarex, where the clinical development program had evolved to use of a different ipilimumab treatment schedules and focused on monotherapy rather than concomitant administration with gp100.
- Retrospective observational studies in the first line setting CA184332 and CA184338.

One Interim summary

- CA184045 safety and efficacy of a subset of patients within an expanded access program (EAP) using ipilimumab 3 mg/kg.

One Population PK (PopPK) report

- Population pharmacokinetic analysis of combined studies (CA184004, CA184007, CA184008, CA184022, CA184024, CA184078), with investigation of exposure-response (ER) in the untreated and treated patients.

Others reports with data

- Line listing of cumulative serious adverse events. The report indicates that the key (legend for abbreviations) is provided on the final page of the report but is not found there, or in the clinical overview documents.

- Supportive data for of immune mediated adverse event analysis for US PI for previously evaluated studies MDX010-20, CA184004, CA184022.

The submitted data was evaluated using TGA adopted EMA Guidelines as follows:

- Guideline on the evaluation of anticancer medicinal products in man EMEA/CHMP/205/95/Rev. 4
- Guidelines for a single pivotal study; Points to consider on an application with 1. Meta analyses 2. One pivotal study. CPMP/EWP/2330/99.

Table 11: Summary of major individual data sources submitted for clinical evaluation (updated following response to TGA request for information)

Report	Phase	Prior systemic therapy	Treatment schedule	Dose mg/kg	PK/ PD	Efficacy (end point)	Safety	Comment
CA184078	I	No	M + C	10	X	Secondary	X	-
CA184078	III	No	C	10	X	Primary	X	-
CA184042	II	Yes	M	10	-	Primary	X	-
MDX10-16	II	Yes	M + C	Mixed	-	Adjuvant setting	X	Terminated prematurely
CA184045	EAP	Yes	M	Mixed	-	Exploratory only for 10 mg/kg; 3 mg/kg submitted after first round questions	X	Dosing changed, Interim
CA184332	Ob	No	M	3	-	Primary	X	Interim post marketing
CA184338	Ob	No	M	3	-	Primary	X	Interim post marketing
PopPK report	mixed	mixed	mixed	mixed	X	ER-OS	ER-irAE	-

"x" indicates relevant data is present; "-" no data is present. Combination (C) Extended Access Program (EAP) Monotherapy (M) Observational (Ob) Pharmacokinetics (PK) Pharmacodynamics (PD) Population PK (PopPK)

Clinical evaluator's recommendation

Following the first round evaluation, the clinical evaluator had numerous questions and was unable to support registration; after the second round evaluation, the clinical evaluator recommended that the benefit-risk favoured registration but noted the significant limitations in the data provided.

Paediatric data

The submission did not include paediatric data.

Pharmacokinetics/pharmacodynamics

Population PK data were submitted and reviewed by the clinical evaluator and separately by a population PK evaluator. The latter's findings were reviewed by the Pharmaceutical subcommittee.

The PopPK analysis collated data from the newly submitted studies and previously evaluated studies (CA184004, CA184007, CA184008, CA184022, CA184024, and CA184078).

Summary of PK data

An extension of the previous PopPK analysis was performed with 3,200 ipilimumab serum concentration values from 785 subjects with advanced melanoma, who were enrolled in the following heterogeneous clinical studies: of these, 528 subjects received ipilimumab monotherapy, while 257 subjects received ipilimumab with DTIC. The dose of ipilimumab varied between trials. All studies included a maintenance phase in contrast to the proposed usage. It was noted that only 14 patients were included in the PopPK analysis that were previously untreated and received ipilimumab 3 mg/kg monotherapy. Furthermore, only 87previously treated patients received monotherapy at the same dose.

The analysis demonstrated that ipilimumab exhibits linear and time invariant PK. The CL and volume of central compartment (VC) of ipilimumab increased with body weight. Ipilimumab CL also increases with baseline LDH, with baseline LDH values less than 675 IU/L (3 times the ULN) being unlikely to have clinically meaningful impact on ipilimumab CL. Age, gender, mild to moderate renal impairment, mild hepatic impairment, immunogenicity, previous cancer therapy and concomitant DTIC administration were not clinically relevant predictors of ipilimumab clearance. Target trough concentrations were set for blockade of B7 molecules;[6] C_{minss} of 3 µg/mL to block CD86 and 20 µg/mL to block both CD86 and CD80. Distributions of predicted C_{minss} showed that the 3 mg/kg dose yielded C_{minss} values that were sufficient for maximal inhibition of CD86, but less than 50% exceeded the 20 µg/mL concentration.

With respect to the current application, the data collated from these heterogeneous studies demonstrated that ipilimumab PK appears similar between previously treated and untreated patients at all dose levels investigated. Importantly, C_{minss} of ipilimumab at the 3 mg/kg dosing was similar for previously treated and untreated patients. However, the small number of patients providing data for the relevant analysis is emphasised.

Efficacy

No randomised, controlled pivotal study was submitted with efficacy data for the proposed indication. The following studies were submitted with the purpose of providing bridging data in support of the proposed posology. Following the receipt of the clinical evaluator's first round report, and after a teleconference with the TGA, the sponsor submitted additional data from the observational studies that was considered to be more directly supportive of the proposed usage.

[6] B7 is a type of peripheral membrane protein found on activated antigen presenting cells (APC) that, when paired with either a CD28 or CD152 (CTLA-4) surface protein on a T cell, can produce a costimulatory signal or a co-inhibitory signal to enhance or decrease the activity of a MHC-TCR signal between the APC and the T cell, respectively. Binding of the B7 of APC to CTLA-4 of T-cells causes inhibition of the activity of T-cells. There are two major types of B7 proteins: B7-1 or CD80, and B7-2 or CD86.

Comment: that there was no randomised controlled data presented to support the first line usage of ipilimumab monotherapy needs to be stated clearly at the start of the Clinical Trials section of the PI, given this is for first line therapy. The current paragraph entitled "Other studies" at the end of a long Clinical Trials section does not convey this.

The studies submitted are considered in order of their relevance to the proposed usage, with figures updated following the additional data submitted.

1. Previously untreated patients treated with 3 mg/kg monotherapy
    - the pooled analysis of Phase II/III studies; 35 patients
    - two retrospective observational studies CA184332 (157 patients), CA 184338 (273 patients)
    - US expanded access program (2155 patients).
2. Untreated patients at high risk of relapse, receiving adjuvant ipilimumab monotherapy 10 mg/kg; not submitted by sponsor but presented at ASCO 2014[7] and therefore taken into account as relevant information from another source.
    - EORTC 18071/CA184029 randomised, double blind, controlled Phase III trial: 475 patients study treatment versus 476 placebo.
3. Untreated patients treated with a higher dose (10 mg/kg), a different regimen which included maintenance treatment with ipilimumab.
    - Phase I monotherapy CA184078 (20 patients).
4. Untreated patients treated with a higher dose (10 mg/kg), a different regimen (including maintenance) of ipilimumab in combination with chemotherapy.
    - Phase III in combination with DTIC versus DTIC alone CA184024.
5. Previously treated patients receiving a higher dose, different regimen.
    - As this usage has already been approved, this is not considered relevant to the extension of indications sought here and will not be discussed further.

Pooled analysis

This analysis was drawn from a range of studies in which patients received 3 mg/kg monotherapy. The clinical evaluator identified from the pooled analyses, 35 patients whose metastatic disease was previously untreated (that is, not 'chemo-naïve') and who were treated with the proposed regimen (monotherapy 3 mg/kg). In response to further clarification of the regimen these 35 patients received, the sponsor (report DCN930076433, dated 7.1.2014), stated that 1 patient received maintenance therapy (that is, not posology for this extension of indications). The Delegate notes that one patient discontinued treatment just days after being included in the study. Across 35 previously untreated subjects, the median OS was 13.5 months, and 1 year survival was 51.5% (2 year survival was 24.4%).

Comment: While this compares favourably with the median OS of 8.9 months (range 0.1 to 47.6 months) and 36% 1 year survival in the DTIC arm of Study CA184024 (see below), the data from these 35 patients were not from a randomised and controlled study as they were drawn from a range of studies, and the number of patients is very small. The limitations of cross study comparisons are also acknowledged.

[7] ASCO 2014; American Society of Clinical Oncology meeting 2014.

The sponsor presented expanded pooled data for 78 subjects (from Studies MDX010-08, MDX010-20, CA184004 and CA184022), which included these 35 patients plus an additional 43 patients who were "chemo-naïve", all of whom received ipilimumab 3 mg/kg monotherapy. Key exclusions in these studies were variously: ocular or mucosal melanoma and any brain metastases or untreated brain metastases. Across 78 chemo-naive subjects, median OS was 13.5 months, and 1 year survival rate was 54.1% (2 year survival was 31.6%, and 3 year survival was 23.7%).

Delegate comment on pooled analyses

1. This application seeks approval for the first line treatment of unresectable or metastatic melanoma not otherwise specified, and the studies' exclusion criteria in this expanded pool variously limited entry of those who have a poorer prognosis that is, brain metastases, ocular or mucosal melanoma. Study CA184024 also excluded patients with brain metastases.
2. Ipilimumab is registered already for use in patients with previous treatment and this is an application for extension to those previously untreated metastatic melanoma, thus data from pre-treated patients provides limited support for the proposed indication. It is noted that the mechanism of action of ipilimumab differs from that of other treatments and a treatment effect could be seen regardless of prior chemotherapy, but the effect after recent prior immunotherapy is less certain.

The most relevant population presented here are those 35 patients who received the dose and regimen proposed, but the findings in both this group and the expanded pool are supportive of an improved OS compared with the current first line therapy, DTIC.

Observational studies

CA184332

CA184332 is a retrospective, observational cohort study of patients in the US receiving 3 mg/kg ipilimumab as first line treatment of unresectable or metastatic melanoma. The purpose of the interim analysis was to summarise key baseline data and OS in patients for whom at least 1 year has elapsed since their initiation of treatment with ipilimumab.

The first analysis submitted was presented for 61 out of 75 patients who matched the characteristics of the population identified in the proposed indication (previously untreated metastatic or unresectable melanoma). Exposure data were not complete, and subsequent therapies (and therefore their potential effect) were not analysed for this report.

Overall survival was defined as the time from initiation of ipilimumab until death from any cause. The median follow-up was 8.5 months and 50.8% of patients had died at the time of this interim analysis. Median OS (was 11.5 months (95% CI: 6.6, -). The estimated 1 year survival rate was 49.3%, although at the time of this interim analysis, the 33% of the patients' survival statuses were not current, that is, the patient was not known to have had died or to be alive within 3 months.

Updated analysis with additional data

In the response to the TGA request for information, and following discussion with the TGA (which requested further data if held in support of the posology), the sponsor provided a "*final abbreviated summary*" which "*summarises the analyses on 157 patients for whom at least 12 months had elapsed since initiation of ipilimumab 3 mg/kg monotherapy as first line treatment*". It was noted that subsequent reports are planned to describe survival at 2, 3 and 4 year milestones.

Of the 157 patients, most had BRAF wild-type (61.8%; 24.8% were untested). 92 out of 142 subjects (65%) received at least 4 induction doses. 18% of subjects discontinued due to toxicity.

Across 157 previously untreated subjects receiving 3 mg/kg, median OS was 11.5 months, and estimated 1 year survival rate was 46.7%. Median OS was 7 months in those with brain metastases, and 14.1 months in patients without metastases.

Comment: this compares favourably with the DTIC median survival from the randomised Phase III trial CA184024. However, these results were from an observational study and are subject to significant potential bias for example the relatively high completion rates are supportive of the tolerability of this usage in this population, but may also indicate significant selection bias.

No data were presented on subsequent therapies, which are particularly important for those who would have been eligible for therapies known to extend OS for example BRAF inhibitors.

The data presented at the round 1assessment were incomplete with ⅓ patients' survival status not known, and the impact of other treatments upon survival unknown. This information was not provided by the sponsor for the updated analysis and is sought now for both observational studies – see Questions for sponsor.

No safety data were presented in this interim analysis.

CA184338

CA184338 is another retrospective, observational cohort study of patients US receiving 3 mg/kg ipilimumab as first line treatment of unresectable or metastatic melanoma. In contrast to the study above, safety data were complete and patients' whose survival data were incomplete were excluded from the safety but not the efficacy analysis.

Updated analysis with additional data

The updated analysis "*summarises the analyses on 273 patients for whom at least 12 months had elapsed since initiation of ipilimumab 3 mg/kg monotherapy as first line treatment*".

Of the 273 patients, 65% were male, 95% were white, and mean age was 63 years at the start of ipilimumab monotherapy. The primary site was cutaneous in 88.3%. At the time of advanced disease diagnosis, 56% were M1c[8] and 12.1% had brain metastases. 81% had an ECOG performance status of 0 or 1 (but in a further 10% ECOG status was unknown). Most patients were BRAF wild-type (66.3%; 15.4% were untested). Median time from initial melanoma diagnosis to advanced melanoma diagnosis was 18.3 months (mean time was 37 months).

Across 273 previously untreated subjects receiving 3 mg/kg, median OS was 14.5 months, and estimated 1 year survival rate was 59.2%. For patients without brain metastases, median OS was 17.5 months.

Comment: these data are more complete than the other observational study and provide some support of the efficacy of the proposed usage. No information about subsequent therapies is provided and at least 19% had BRAF mutations and at this time would have been eligible to participate in clinical trials for BRAF or MEK inhibitors, or had access to those already registered. The quality of the data is limited by the retrospective nature of the study, that it was uncontrolled, with the potential to introduce bias. However, the completion rate does indicate that the treatment was tolerated and the median survival of 14.5 months compares favourably with the control DTIC arm of Study CA184024.

[8] M1c is defined as Stage IV Melanoma with other distant metastasis or any distant metastasis with elevated LDH.

Extended access program (interim summary for CA184045)

The patients in this expanded access program had received prior treatment (which could include ipilimumab), and the regimen was 10 mg/kg until a subsequent amendment mandated a 3 mg/kg dose level. A further amendment mandated the collection of survival data beyond completion of the access program, which could end with death, discontinuation of treatment or registration of the treatment in the relevant country. Prior to this amendment, the causes of death were not collected for all patients, and for the initial analysis presented, 30% of patients' survival status were unknown.

Some patients entering were pre-treated, while others entered the extended access program (EAP) following completion of a clinical trial with ipilimumab; the latter were excluded from the analysis as AEs would not have been fully assessable. After Amendment 3 (March 2010), subjects enrolled were treated with 3 mg/kg ipilimumab induction followed by re-induction (if eligible); maintenance dosing was not offered with the 3 mg/kg dose. Earlier subjects receiving 10 mg/kg ipilimumab were still eligible for maintenance dosing at 10 mg/kg and were also eligible for re-induction following the approval of this amendment.

However, the data in the dossier initially presented by the sponsor from this expansion access program was for those receiving the 10 mg/kg regimen not the 3 mg/kg regimen. In response to the clinical evaluator's request for the data on the 3 mg/kg dose level, the following data were provided. 92% had an ECOG of 0 or 1, despite 33.2% having brain metastases.

The median OS for the 2,155 out of 2,276 patients analysed was 7.6 months and 1 year survival estimated at 45%. The median follow-up was relatively short (6.1 months), and there was a high dropout rate. 619 patients were excluded from the analysis as the last amendment in August 2012 to collect OS was not approved, and 27% discontinued due to cessation of the access program upon approval in the country. When those with brain metastases, ocular or mucosal melanoma were excluded (leaving 1,240 patients in the analysis), the median survival increased to 10.2 months.

No data were provided on subsequent therapies, particularly those that might influence survival.

Comment: it is unclear why the median duration of follow-up was so short when it is stated "*Subjects who received their first dose after 27 June 2011 were excluded to ensure that only those who had the opportunity to be followed up for at least one year are included in the OS analysis*" It would be reasonable to expect that the 2 year OS data are available and these are requested in the questions for the sponsor.

There are substantial missing data due to the variable agreement to Amendment 6 by different regions, which highlights the challenges of using interim or post-marketing data to support registration and ensuring adequate, relevant, high quality data are collected. Given this is one of the few groups where treatment occurred in the correct population and with the proposed dose and regimen, this deficiency is important. The Delegate is in agreement with the clinical evaluator's second round assessment that this EAP was not designed to answer pre-specified efficacy and safety questions, and it is difficult to determine whether it can be used to support registration.

EORTC 18071/CA184029

Study in untreated patients with high risk of relapse (Stage III disease) undergoing adjuvant treatment with 10 mg/kg ipilimumab, with maintenance treatment.

At the recent annual ASCO meeting, 2014, Eggermont AM et al. presented initial safety data from a randomised, double blind Phase III EORTC 18071 (CA184029) study which investigated the benefit of adjuvant ipilimumab 10 mg/kg monotherapy with a

maintenance phase versus placebo in previously untreated patients at following complete resection of Stage III melanoma (please refer to the downloadable slides from the presentation of the referenced abstract for the information discussed below[9]).

Comment: this population was untreated, and at very high risk of relapse as evidenced by the historical rates of relapse in these patients (up to 89% in Stage IIIc) thus essentially many have metastatic disease not detectable by conventional staging. The similarities to the proposed usage are the monotherapy in a previously untreated population, many of whom have micrometastases; the differences are the higher dose of and the maintenance ipilimumab therapy and the absence of detectable metastases. This large randomised trial provides evidence for the safety and efficacy of ipilimumab monotherapy, noting these key differences. The safety issues are significant (especially in the context of this application and are discussed below), but the statistically significant decreased relapse rate observed in the ipilimumab treated arm supports efficacy in an untreated population.

Studies in patients receiving 10 mg/kg ipilimumab, maintenance treatment Study 184078 – Phase I

This PK study enrolled patients to 3 arms: 2 combining chemotherapy with ipilimumab 10 mg/kg versus ipilimumab 10 mg/kg alone, with maintenance continued for all arms (10 mg/kg) every 12 weeks until progression or toxicity developed. Efficacy was a secondary outcome.

A total of 59 patients were randomised, with 20 receiving ipilimumab alone (10 mg/kg); 5 patients (25%) in the ipilimumab alone group had a response, but there was no control arm (consistent with a Phase I trial) to compare response.

Comment: these data do not lend support for the proposed usage that is, extension into use first line because the dose and schedule were different and the number of patients in the ipilimumab alone arm was too small to draw conclusions.

Studies in untreated patients receiving 10 mg/kg ipilimumab with chemotherapy

Study CA184024

This Phase III, multi centre, randomised, double blind, 2 arm study in patients with previously untreated Stage IIIc, N3 (unresectable) or Stage IV melanoma receiving DTIC plus 10 mg/kg ipilimumab versus DTIC with placebo and includes a maintenance phase. Details of the trial are in Attachment 2.

The median survival for the DTIC arm was 8.9 months (range 0.1 to 47.6 months); the survival rate (with 95% CI in brackets) at 1 year with DTIC was 36.3% (30.4, 42.4), at 2 years 17.9% (13.3, 22.8) and at 3 years was 12.2% (8.2, 16.5).

Delegate comment: These data provided a baseline for determining overall survival in untreated patients receiving DTIC for comparison with the other non-randomised studies above. However, the combination of 10 mg/kg ipilimumab with DTIC plus maintenance does not provide efficacy support for the proposed monotherapy usage, the dose proposed (3 mg/kg) nor the regimen (4 cycles, no maintenance). Thus, while there is some indication of an improved survival rate as combination therapy, this will not be considered further.

Study CA184042 (Phase II interim report)

An interim report dated 07 Dec 2011 was submitted from CA184042 ,described as an 'ongoing' two stage modified Gehan designed Phase II trial to study the potential tumour

[9] Ipilimumab versus placebo after complete resection of stage III melanoma: Initial efficacy and safety results from the EORTC 18071 phase III trial http://meetinglibrary.asco.org/content/130118-144

response and safe use of ipilimumab 10 mg/kg monotherapy (4, 3 weekly doses with potential maintenance phase) in subjects with Stage IV melanoma with brain metastases.

The trial is summarised in Attachment 2, and the Delegate is in agreement that with the clinical evaluator that while there is some support for the efficacy of ipilimumab 10 mg/kg +/- maintenance schedule in disease control in this population, that overall this study cannot be said to provide evidence in support of the proposed usage. This is because there were very small numbers of patients (with even fewer who completed the induction treatment (16 out of 72; 13 of whom went on to maintenance treatment which is not the proposed usage here) and many were previously treated (> 70%), the dose and schedule were different, and this was a non-randomised trial, with potential bias.

Summary of efficacy

The support for the proposed usage is indirect, with no randomised clinical trials undertaken in the identified population testing ipilimumab monotherapy at the proposed 3 mg/kg dose, without maintenance. The application is variously reliant upon extrapolation of efficacy from a range of studies (pooled analyses, retrospective observational studies) as well as those using other dose levels and regimens (for example combination with chemotherapy) and additional information is drawn by the Delegate from use in an earlier adjuvant setting. Efficacy has been established in previously treated patients, and there is no plausible reason why it would not be effective in the first line treatment, given its significantly different and independent mode of action from the current first line, DTIC.

The support for its first line efficacy is drawn from:

1. Retrospective observational studies where the same dose and same regimen in a previously untreated population with metastatic disease comes from. In the larger cohort (CA184338), the median OS with ipilimumab monotherapy was 14.5 months (17.2 months in those without brain metastases) compared with 8.9 months in the cross study control group treated with DTIC in Study CA184024. In the second observational study (CA184332), the median OS was 11.5 months, with median OS rates of 14.1 months in patients without brain metastases and 7 months in those with brain metastases. There was a major difference in the OS, the completion rates for the 4 treatments and discontinuations due to AEs between the two cohorts and the reasons are unclear. There is a risk of significant potential bias such as selection bias in such retrospective studies. Although there were significant methodological issues, and the data do suggest that there is a consistent treatment effect, with an improved median OS with ipilimumab monotherapy compared with the DTIC control arm in Study 184024.
2. Support for efficacy of ipilimumab monotherapy can be derived from the results in a previously untreated cohort at high risk of relapse (albeit with a higher dose plus maintenance), where adjuvant ipilimumab significantly decreased the rate of relapse; however, there was significant toxicity noted in this study (which is the only randomised study assessing safety and efficacy of ipilimumab monotherapy), some of which was irreversible (see Safety section below).
3. Study CA184024 compared ipilimumab in combination with DTIC versus DTIC alone in previously untreated patients. As noted, both the regimen (combination with chemotherapy and maintenance dosing) and dose differed for the combination arm compared with the proposed usage, limiting the conclusions that can be drawn for ipilimumab monotherapy; the findings are however, generally supportive of there being a benefit of first line ipilimumab in previously untreated patients with metastatic or unresectable melanoma.

4. PK and PD studies were presented to support the effects of ipilimumab being independent of prior treatment, DTIC and that the efficacy of 3 mg/kg was similar to that of the 10 mg/kg dose level.

Future data likely to provide direct supportive data for the proposed usage

Post-marketing study

There is a post-marketing study underway comparing the safety and efficacy of the 3 mg/kg versus 10 mg/kg (Study CA184169) in both previously treated and untreated patients with metastatic or unresectable melanoma which should clarify the relative safety and efficacy between the two different dose levels (for details see Attachment 2). The hypothesis is that 10 mg/kg is superior to 3 mg/kg. The sponsor has stated this study report "will be considered for submission to TGA when the results become available". This is not considered adequate and given the lack of direct comparative data overall and particularly with respect to the higher versus the lower dose (important information for the prescriber and the patients), the submission of this study for evaluation is a condition of registration (see conditions of registration). Furthermore, it is noted that the sponsor has amended the protocol now to have no interim safety analysis (thus was unable to provide the safety analysis requested by the clinical evaluator), and now no analyses will be presented until all patients have been followed for at least 2 years. This has meant a delayed analysis date until December 2016 with a proposed CSR then only being available in December 2017, some 13 months later. This approach means randomised, comparative safety data (which is currently lacking for this application) from this important confirmatory trial which would provide regarding safety data to inform the PI about the proposed usage will be significantly delayed. The sponsor reports that the Data Monitoring Committee has not identified any new safety issues. The opinion of the ACPM is sought as to whether an interim safety analysis ought to be a condition of registration, given the absence of any safety data provided to support the proposed usage directly.

Safety

As there is no pivotal trial submitted with randomised controlled data in support of safety, evidence for safety with the proposed usage is drawn from;

1. The randomised controlled EORTC 10871/CA184029 adjuvant study of 10 mg/kg ipilimumab monotherapy versus placebo. As the only study available providing randomised data for ipilimumab monotherapy in previously untreated patients, this study provided very important information about the risks, even allowing for the use of a higher dose and the earlier high-risk adjuvant setting. Of note, with the exception of the hepatic irAEs the reported rates for total and individual irAEs were much higher than for Study 184024, the only other study with randomised data in this untreated population, which used the same dose of ipilimumab but in combination with DTIC. There is not a clear explanation for these differences. These differences are discussed in the CER, and are evident in the 2 tables summarizing the irAEs from each trial are in Tables 12 and 13. The key signals from EORTC 10871/CA184029 compared with CA184024 were:
    a. A higher rate of total irAEs
    b. 5 drug related deaths in the study arm
    c. 6 drug related GI perforations versus 3 non related in the placebo
    d. a high rate (37.6%) of endocrine AEs, with 44% not resolving and a slow resolution when this did occur (median 13.9 to 186 weeks)
    e. a high rate of grade 2-4 irAEs not resolving
        i. endocrine 44%

ii. skin 11%

iii. GI 6%

iv. hepatic 5%.

Table 12: Summary of irAEs on EORTC 18071 (adjuvant use of 10 mg/kg ipilimumab monotherapy in previously untreated patients with a maintenance phase). (This data is copied directly from Slide 12 of the oral presentation for the referenced abstract.)

	% Patients					
	Ipilimumab (n=471)			Placebo (n=474)		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Any irAE	**90.4**	**36.5**	**5.5**	38.6	2.3	0.2
Dermatologic	**63.3**	**4.5**	**0**	20.9	0	0
Rash	34.4	1.3	0	11.0	0	0
Gastrointestinal	**46.3**	**14.9**	**1.1**	17.7	0.6	0.2
Diarrhoea	41.4	9.6	0	16.7	0.4	0
Colitis*	15.9	6.8	0.8	1.3	0.2	0
Endocrine	**37.6**	**7.9**	**0.6**	6.5	0	0
Hypophysitis	18.3	4.7	0.4	0.4	0	0
Hypothyroidism	8.9	0.2	0	0.8	0	0
Hepatic	**25.1**	**7.9**	**2.8**	4.4	0.2	0
LFT increase	19.7	3.8	1.5	4.0	0	0
Neurologic	**4.5**	**1.1**	**0.8**	1.9	0	0
Other	**23.6**	**7.4**	**0.4**	4.4	1.7	0

*Gastrointestinal perforations: Ipilimumab, 6 related (1.3%); placebo, 3 unrelated (0.6%). LFT = liver function test.

Table 13: Summary of irAEs from CA184024 as presented by the sponsor

	Ipi+DTIC (N = 247)	DTIC (N = 251)
Subjects with any on-study irAE (n, %)	**187 (75.7)**	**77 (30.7)[a]**
Grade 3/4 irAE	92 (37.2)	5 (2.0)
Serious irAE	91 (36.8)	3 (1.2)
Death due to irAE (n %)	0	1 (0.4)
Gastrointestinal irAEs	88 (35.6)	42 (16.7)[a]
Grade 3/4	14 (5.7)	0
Liver irAEs	91 (36.8)	15 (6.0)
Grade 3/4	69 (27.9)	5 (2.0)
Endocrine irAEs	7 (2.8)	2 (0.8)
Grade 3/4	0	0
Skin irAEs	106 (42.9)	26 (10.4)
Grade 3/4	8 (3.2)	0
Other[b] irAEs	36 (14.6)	12 (4.8)

Source: Appendices 6.11, 6.18, 6.20, 6.21, 6.22, 6.23, 6.24

[a] One Grade 5 (fatal) event was reported in the DTIC group (GI hemorrhage).

[b] Includes blood, eye, immune system, infections, renal, and respiratory systems

irAE = immune-related adverse event

Comment: This study raises issues about the safety profile of ipilimumab when used in a previously untreated population, as the rates of irAEs are higher than reported in other studies. While these risks may be considered unacceptable in the adjuvant setting (albeit in those at very high risk of relapse that is, a high likelihood of having metastatic disease beneath the limits of detection by conventional imaging), for those presenting with metastatic disease, the alternative of disease progression is worse. However, it is important that these risks are presented to allow an informed decision. The sponsor has argued that the patients in this trial differ significantly from those with metastatic disease (while simultaneously arguing that patients with metastatic disease are on a continuum), but the Delegate considers this population, many of whom are likely to relapse, are very close to those who are newly diagnosed with detectable metastatic disease. Whilst the limitations of uncontrolled cross study comparisons are noted and the presentation of information as an oral abstract of the referenced study, in general the toxicity observed within this adjuvant study of healthy patients was numerically higher than that presented in CA184024 (same ipilimumab dose). Significantly, there were five deaths within this healthy population and six treatment related GI perforations. In addition, the number of irAEs observed was numerically higher than reported in CA184024.

The Delegate believes this information should be captured in the PI to inform both prescribers and the CMI for consumers, even though the proposed usage is for a lower dose and in an adjuvant setting, and seeks the advice of the ACPM as to how best to do this. Currently this provides the highest quality safety evidence in untreated patients receiving ipilimumab monotherapy; it is possible that the submission of an interim safety analysis from Study CA184169 proposed as a condition of registration by the Delegate, which will have randomised data from use of the 3 mg/kg dose in untreated patients,

could be used to revise these rates in the metastatic previously untreated patients if the results differ.

2. A pooled analysis of 55 previously untreated patients presented by the sponsor comprising 35 patients receiving 3 mg/kg monotherapy (20 from trial MDX-010-08, and 15 from CA184004, CA184022) plus 20 patients who received 3 mg/kg plus DTIC in MDX-101-08 trial. The sponsor has stated that immune mediated AEs were not collected in patients from CA184004 and CA184022, as per the protocol for those trials. Thus there are 20 patients for whom more complete safety data are available at the proposed usage (3 mg/kg monotherapy). The inclusion of the combination with chemotherapy was done to capture all patients receiving the 3 mg/kg dose in the Phase II/III studies.

3. 430 patients treated in the retrospective observational studies CA184332 and CA184338; the safety data are incomplete as stated in the sponsor's response: an updated percentage of patients' whose survival status was known was not stated in the response for each cohort. The sponsor is requested to provide the proportion of patients whose survival status or cause of death was known for each cohort. The methods of collecting safety data changed over time with amendments, and are summarised in a table taken from the sponsor's response (see Table 14). The safety data were collected retrospectively and the detail of that information varied between the two cohorts. This makes comparisons with other trial populations such as those with previously treated metastatic melanoma difficult. Data from the CA184332 cannot be interpreted in a meaningful way due to the incomplete collection whereas more complete data is available from the Study CA184338. In the latter, where 212 out of 273 subjects (78%) received at least 4 induction doses and 10.6% of subjects discontinued due to toxicity. irAEs occurred in 49.8% with 12.5% Grade 3 or 4; drug related SAEs were reported as occurring in 13.9%. It is notable that even with the limited data collected; the rates of discontinuation due to AEs reported in the CA184332 were higher at 28% versus 19.5% in CA184338.

Table 14: Comparison of safety data collection in the observational studies versus standard clinical trial methodology

	Clinical Trial Definitions/Methodology	CA184332	CA184338
AE reporting	All AEs that occurred during the first-line ipilimumab therapy (the interval between documented start and stop dates of first-line ipilimumab therapy) were recorded	Same as clinical trial definitions but collected retrospectively	Only disease-related AEs and AEs related to anti-cancer treatment ("treatment-related AEs") were reported
AE coding	Coded using MedDRA	Not coded[a]	Coded using MedDRA
SAE reporting	Any AE or adverse reaction that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect	AEs that either were documented as being "serious" in the patients' charts or were AEs that led to a hospital/emergency room visit or death	Same as clinical trial definitions but collected retrospectively

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities, SAE, serious adverse event

[a] AEs were categorized as skin, liver, endocrine, neurological, or gastrointestinal AEs based on a list of pre-defined events (refer to SCS Section 2.1[25])

Comment: the data from CA184338 indicate similar rates of adverse events as reported in the previously treated study MDX-010; however, these data have not been collected as rigorously as in a clinical trial and there is significant potential for underreporting. The sponsor is asked to clarify whether there were any deaths attributable to treatment.

Table 15: Overall summary of safety (CA184332 and CA184338)

	NUMBER OF PATIENTS (%)			
	CA184332 (N=157)	CA184338 (N=273)		
		Any Grade	Grade 3	Grade 4
All AEs	100 (63.7)	164 (60.1)	45 (16.5)	8 (2.9)
Drug-related AEs	Relationship not assessed	147 (53.8)	38 (13.9)	5 (1.8)
irAEs	Not analysed	136 (49.8)	31 (11.4)	3 (1.1)
Deaths	83 (52.2)[a]	142 (52.0)[a]		
Death related to melanoma	78/83 (94.0)	127/142 (89.4)		
Other causes	2/83 (2.4)	8/142 (5.6)		
Unknown/missing	3/83 (3.6)	7/142 (4.9)		
SAEs	46 (29.5)	51 (18.7)	33 (12.1)	7 (2.6)
Drug-related SAEs	Relationship not assessed	38 (13.9)	26 (9.5)	5 (1.8)
AEs Leading to Discontinuation[b]	28 (28.0)	31 (11.4)	18 (6.6)	4 (1.5)
Drug-related AEs Leading to Discontinuation	Relationship not assessed	29 (10.6)	18 (6.6)	3 (1.1)

Abbreviations: AE, adverse event; irAE, immune-related adverse event; SAE, serious adverse event

[a] Deaths were as of the most recent follow-up in both studies and were not limited to those that occurred during induction only. "Other causes" of death in CA184332 were acute myocardial infarction and a death that was described as "not related to melanoma". "Other causes" of death in CA184338 were accidental death (3 patients) and single reports of heart failure/renal failure, congestive heart failure/myocardial infarction, pneumonia/sepsis, stroke, and pulmonary embolism.

[b] Action taken to manage AE and outcome of AE were assessed among those patients in CA184332 who had at least one of the following AEs: skin, liver, endocrine, neurological, gastrointestinal, SAEs, or any other AEs (n=100).

4. The expanded access program had large amounts of missing data (30% were not followed up for survival, and presumably therefore for other parameters including AEs) and therefore cannot be relied upon for accuracy in reporting safety data nor to provide any new safety signals.

Other safety matters

During the evaluation of the data presented in the dossier, the clinical evaluator had many questions of the sponsor regarding AEs and their classification in CA184024. In recognition that this trial does not provide direct safety evidence for the proposed usage due to the combination with chemotherapy, the questions were limited to examples to understand better the approach the sponsor adopted, rather than a comprehensive listing of all queries. In general, these examples were limited to the higher grade AEs, including questions about Grade 5 (deaths) classification.

In response to the clinical evaluator's questions, the sponsor explains there can be many sources of data used by the sponsor in presenting the narrative, but the final assessment by the sponsor physician determines the grading and attribution of causality; this information is primarily taken from Oracle Clinical Study database. In particular, the sponsor physician determines the immune mediated events which are distinct from immune related AEs (which are possibly, probably or definitely related by the investigator) and determine the attribution to treatment after excluding any other potential causes that might contribute and confound (for example infection, progression). The sponsor indicates that the Common Terminology Criteria for Adverse Events (CTCAE)

version 3 is used rather than the newer version 4 for consistency of adverse event grading criteria between earlier and later trials.

Overall, while the explanations presented by the sponsor could be followed, there appears to be room for debate in some of the interpretations, with both the Delegate and the clinical evaluator considering the approach adopted can potentially downgrade AEs, including imAEs. This is illustrated by the sponsor's response to a case where the clinical evaluator queried the classification of AEs. The CTCAE version 3 classifies Grade 2 diarrhoea as; 4-6 times increased frequency of stools above baseline, requiring intravenous (IV) fluids for < 24hours, and not interfering with ADLs. Grade 3 includes stool frequency > 6 above baseline, hospitalisation, fluids > 24 hours and interference with ADLs. Between days 53 to 169, the patient was hospitalised on 3 occasions due to colitis and diarrhoea, which failed repeated tapering of steroids over several months, required TPN administration during more than one admission and necessitated infliximab (symptoms were reported to have resolved on day 169). While the sponsor has graded this as a serious adverse event, it maintains the grading of imAE as 2, stating that hospitalizations and administration of TPN (IV fluid > 24 hours) reflect a clinical management decision rather grade the severity of the precipitating clinical adverse event. The sponsor's assertion that it is primarily stool frequency that dictates the grading, is considered an incorrect interpretation of the grading system by the Delegate. There is no weighting of the events indicated in the CTCAE guide listing of Grade 2 criteria; the grading takes into consideration the treatments required for resolution (IV fluids, hospitalisation), the impact on the patient (ADLs) as well as the signs or symptoms.

Comment: this study does not provide direct evidence for the safety of the proposed usage and the sponsor has indicated clearly that this application is not for use of ipilimumab in combination with DTIC. Therefore, a further exploration or discussion of the AEs from this study is not considered relevant to the application but would be required if the sponsor were to apply for combination therapy with DTIC as first line. It does, however, raise the possibility that there are different approaches to the CTCAE grading system for presenting the toxicity of immune therapies, which may lead to an underestimate of the severity of the events and that the SAEs may be a better guide to establishing toxicity.

Safety summary

The safety profile of ipilimumab in pre-treated patients is well known, with a propensity for irAEs: skin gastrointestinal, hepatic and endocrine. Other immune mediated AEs have also been noted at lower frequencies. As there was no pivotal trial, the sponsor provided safety data from retrospective observational cohort studies and pooled analyses using the proposed dosage and regimen, as well as studies where ipilimumab was used at a higher dose and those where it was given in combination with chemotherapy.

While these retrospective studies did not provide any new safety signals, the design and methodology would have meant this was unlikely to detect them. Many of the datasets were incomplete, with uncertainty about the adverse event reporting rates (including deaths) and attribution of causality. By contrast, the randomised controlled trial, EORTC 10871/CA184029, identified strong safety signals including deaths, gastrointestinal perforations, and for almost all irAEs, higher frequency and degrees of irreversibility of the irAEs with ipilimumab 10 mg/kg monotherapy in an untreated population than reported elsewhere with any other usage. Furthermore, there were higher rates of irAEs than reported for the CA184024 trial, which combined the same dose of ipilimumab with chemotherapy in those with previously untreated metastatic disease.

The risks of these irAEs are significant, and many appear irreversible and the PI does not currently reflect this sufficiently. Given the deaths, GI perforations, rates of diarrhoea and

colitis observed with ipilimumab usage, (even before considering the data from the adjuvant study), the Delegate considers a boxed warning would have been appropriate. It is noted that such a warning is present in the Canadian monograph and the US label. The ACPM is requested to consider this, as the best safety data for use in previously untreated patients indicates a potentially high risk.

Benefit-risk

The Delegate still considers that in the metastatic setting, patients may choose to take the risk of such adverse events, given the alternative is their disease progressing unabated. It is important these risks are reflected in the PI, so that prescribers can provide information to patients who can then make an informed decision.

The sponsor has not provided direct evidence of efficacy at the scheduled 3 mg/kg dose or the schedule proposed, so relies on various indirect pieces of evidence. Overall, while there are deficiencies identifiable in all of these pieces of evidence, they all point to an increased chance of improving overall survival compared with historical or cross study comparisons for the currently approved alternative of dacarbazine chemotherapy. As with the safety data, the Delegate considers it important that the limitations (that is, no Phase III study) are conveyed clearly in the PI to inform prescribers.

Although there have been other agents such as BRAF inhibitors that have demonstrated an improvement in survival, only half of patients with unresectable or metastatic melanoma have a BRAF mutation. Thus there is significant unmet need, and the only approved alternative is DTIC or fotemustine chemotherapy.

Risk management plan

The Office of Product Review has accepted the EU-RMP Version 8.2 (data lock point 18 September 2012) with ASA version 1 dated 29 November 2013.

Risk management plan

The Delegate is in agreement with the RMP evaluator that optic neuritis should be added to the list of identified risks in the RMP.

A number of recommendations for the RMP have been provided by the RMP evaluator and the sponsor should address these matters in the Pre-ACPM Response and follow up where appropriate with the TGA.

Delegate's considerations

Data deficiencies /limitations

No pivotal trial was presented in support of the proposed usage to inform directly regarding the safety and efficacy of the proposed usage. Other deficiencies have been cited in the body of the report.

Questions for the sponsor

1. For each of the 2 observational studies where patients received 3 mg/kg ipilimumab monotherapy, the sponsor is requested to state the percentage for whom the survival status was unknown at the time of the updated analysis. For what percentage in each study is the safety data complete?
2. The sponsor is requested to provide updated 2 year survival data for the EAP. If this is not available, the sponsor is requested to provide a justification.
3. The sponsor is requested to indicate whether the education program required before being permitted to prescribe when the compassionate access program is still in place.

If not, what education is offered to prescribers in its place? Does this prompt prescribers to report adverse events?

Conditions of registration

The following are proposed as conditions of registration

1. Implementation of the Yervoy EU-RMP version 8.2 (data lock point 18 September 2012) with Australian-specific Annex version 1 dated 29 November 2013 and any future updates as a condition of registration.
2. Submission of the following clinical trial(s) as Category 1 submissions within 6 months of completion which were designed to evaluate
    a. Both an interim safety analysis and subsequently the complete CSR for Study CA184169 (the post-marketing study underway comparing 3 mg/kg versus 10 mg/kg).

Proposed action

The Delegate had no reason to say, at this time, that the application should not be approved for the following indication:

> *Yervoy, as monotherapy, is indicated for the treatment of patients with unresectable or metastatic melanoma.*

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. Whether an interim safety analysis for CA184169; 3 mg/kg versus 10 mg/kg in previously untreated and treated patients; should be mandated as a condition of registration given the absence of any randomised, controlled safety data to support the proposed usage. After an amendment, the sponsor now plans to delay any analyses until all patients have been followed for a minimum of 2 years, and to submit a CSR some 13 months after this. Thus, safety data will also be delayed until this time (safety problems usually occur early).
2. Whether a boxed warning is warranted given the deaths, GI perforations, rates of severe and potentially fatal or irreversible immune-related AEs.
3. How best to reflect the safety signals from the adjuvant study to inform regarding the risk in previously untreated patients, given no other randomised safety.

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Introduction

The sponsor acknowledges the Delegate's request for advice of 06January 2015 and the recommendation to approve the sponsor's proposed indication. The sponsor also acknowledges the second round clinical evaluation recommendation to approve this submission based on a favourable benefit/risk ratio.

Ipilimumab is recognised globally as a major advance in the treatment of patients with unresectable or metastatic melanoma with long-term OS extending beyond 5 years.[10] Over

[10] Schadendorf D, et al: Pooled analysis of long-term survival data from Phase II and Phase III trials of ipilimumab in metastatic or locally advanced, unresectable melanoma [abstract]. *Eur J Cancer* 2013, 49(suppl):24LBA.

15,000 patients with unresectable or metastatic melanoma have been treated globally with ipilimumab as a first line therapy and its use in this setting is currently endorsed by the NCCN and ESMO clinical practice guidelines for the diagnosis, treatment and follow-up of patients with cutaneous melanoma.[11] [12] Country level guidelines that recommend ipilimumab as an option in previously untreated patients include Germany and Switzerland.

Ipilimumab has received regulatory approval as a first line therapy at a dose of 3 mg/kg as monotherapy in patients with unresectable or metastatic melanoma in Europe, Canada, USA, Switzerland, Singapore, Israel, Argentina, Chile, Colombia, Brazil, Peru and South Korea. The broad acceptance of ipilimumab 3 mg/kg as a standard of care in the first line metastatic setting is further reflected in the design of ongoing multinational clinical trials of new immunotherapies such as pembrolizumab and nivolumab where ipilimumab is used as the preferred comparator.

Clinical trial data consistently show a plateau in survival curves after 2 to 3 years, with approximately one fifth of patients having long-term durable survival, as confirmed with 10 years' follow-up for some patients.[10],[13],[14],[15] This pattern of effect has also been consistently observed in large scale named patient and expanded access programs in Australia, Germany and Italy.[16],[17],[18]

Overview of application

The purpose of this application is to seek approval for the use of a 3 mg/kg monotherapy dose of ipilimumab as first line therapy in patients with unresectable or metastatic melanoma. The sponsor wishes to clarify for the ACPM that it is not seeking an indication for 10 mg/kg monotherapy dose in this population, nor is it seeking an indication for use of a 3 mg/kg or 10 mg/kg dose in the adjuvant setting. Clinical data provided with this application at the 10 mg/kg dose was used to support proof of concept of efficacy. Any request by the sponsor for use of this dose will be submitted as a separate and distinct application to allow the TGA to fully evaluate the benefits and risks of therapy at this dose and in this patient population.

While no randomised comparison with ipilimumab 3 mg/kg is available, multiple data sets from clinical studies, which include an accumulated total of over 500 patients, confirm a similar durable overall survival benefit, as well as similar safety, when ipilimumab 3 mg/kg monotherapy is used as first line treatment compared to later lines and thus support this submission. The data submitted with this application across clinical efficacy, pharmacokinetics (where consistency in pharmacokinetic data between untreated and previously treated subjects was demonstrated), pharmacodynamic effects and safety and tolerability, all indicate that the effects of 3 mg/kg ipilimumab administered as monotherapy is independent of prior therapy.

[11] Coit, D. G.et al. "NCCN Melanoma guidelines, version 4.2014." *J Natl Compr Canc Netw* 2014;12: 621-629.
[12] Dummer, R et al, on behalf of the ESMO Guidelines Working Group. Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology* 2012; 23: vii86–vii91.
[13] Lebbé C, et al Long-term survival in patients with metastatic melanoma who received ipilimumab in four phase II trials [abstract]. *J Clin Oncol* 2013, 31(suppl):9053.
[14] Wolchok JD, et al Four-year survival rates for patients with metastatic melanoma who received ipilimumab in phase II clinical trials. *Ann Oncol* 2013, 24:2174–2180.
[15] Maio M, et al: Four-year survival update for metastatic melanoma patients treated with ipilimumab plus dacarbazine in phase 3 study CA184-024 [abstract]. *Ann Oncol* 2012, 23(suppl 9):1127P.
[16] Alexander, M et al. Ipilimumab in pretreated patients with unresectable or metastatic cutaneous, uveal and mucosal melanoma. *MJA*, 2014; 201: 49-53.
[17] Eigentler, T.K et al. Effectivenss and tolerability of ipilimumab: Experiences from 198 patients included in an a named-patient program in various daily-practice settings and multiple institutions. *J Immunother* 2014; 37: 374-381
[18] Ascierto, P, A et al. Clinical experience with ipilimumab 3 mg/kg: real-world efficacy and safety data from an expanded access programme cohort. *Journal of Translational Medicine*, 2014; 12:116

Discussion on efficacy

While no randomised comparison with ipilimumab 3 mg/kg is available, this submission includes OS from a considerable number of previously untreated and chemo-naive patients receiving ipilimumab 3 mg/kg, including from two large scale observational first-line studies (CA184338[19] and CA184332[20]) and from pooled Phase II/III studies. This data provides substantial evidence that ipilimumab has at least similar efficacy in a first line metastatic clinical setting, compared to later lines. The sponsors approach to this submission within this context was discussed with the TGA at two separate meetings and minutes from these discussions were provided this response.

As acknowledged earlier by the delegate, the median OS and 1 year OS rates in all data sets, which include a total of more than 500 patients, were numerically superior to OS of patients receiving DTIC in the control arm of CA184024[21] and were superior to the OS predicted for these cohorts based on historical controls. This consistent observation of superior OS was observed despite the fact that in CA184338[19] and CA184332[20], 12% and 34% of patients, respectively, compared to < 2% of patients in CA184024, had evidence of brain metastases at baseline, which is known to be associated with poorer prognosis. These results were acknowledged by the delegate in addition to the survival data reported from the two observational studies CA184338 and CA184332.

In response to the Delegates first question to the sponsor in relation to the percentage of patients for whom survival status was known at the time of the updated analysis from these studies, the sponsor confirms that survival was known for all subjects included in the final analyses (either patients had died, or they were known to be alive at a certain date, the "last known alive date"). The analyses for both studies included only subjects who had initiated treatment 12 months or longer prior to data cut-off, to ensure patients could theoretically be followed for at least 1 year. However, subjects may have died earlier, or may have been lost to follow up earlier. Median follow up and currentness of overall survival information (that is how close the "last known alive date" is to the cut-off date) is presented for the two studies in the CSRs and is briefly summarised below. Currentness of survival data from both studies is included. In summary, the data show that survival results are mature for 1 year rates, but further follow up is required to more accurately estimate 2 year survival rates.

- In study CA184338, as of the date of data cut-off (20 December 2013), the median follow-up was 12.2 months from ipilimumab initiation. The interquartile range (25% to 75%) was 6.6 to 15.9 months (that is 25% had more than approximately 16 months follow-up) and a total of 142 of 273 patients (52.0%) had died. More than 50% of subjects had either died or had last known alive date less than 3 months prior to data cut-off.[19]
- In study CA184332, as of the date of data cut-off (20 December 2013), the median follow-up was 8.5 months from ipilimumab initiation (interquartile range [25% to 75%] was 2.86 to 14.99 months) and 83 of the 157 patients (52.2%) had died. About 80% of subjects had either died or had a last known alive date less than 3 months prior to data cut-off.[20]

[19] CA184338 Final Clinical Study Report. A Multisite Retrospective Observational Study of US Patients with Unresectable or Metastatic Melanoma Receiving Ipilimumab (Yervoy) as First-line Therapy. Bristol-Myers Squibb Company; 2014. Document Control No. 930079470.
[20] CA184332 Final Clinical Study Report. A Multisite Retrospective Observational Study of US Patients with Unresectable or Metastatic Melanoma Receiving Ipilimumab (Yervoy) as First-line Therapy in a Community Practice Setting. Bristol-Myers Squibb Company; 2014. Document Control No. 930079411.
[21] CA184024 Final Clinical Study Report. A Multi-Center, Randomised, Double-Blind, Two-Arm, Phase III Study in Patients with Untreated Stage III (Unresectable) or IV Melanoma Receiving Dacarbazine Plus 10 mg/kg of Ipilimumab (MDX-010) vs. Dacarbazine with Placebo. Bristol-Myers Squibb Company. Document Control No. 930053924.

Discussion on safety

Since registration of ipilimumab in June 2011, Australian oncologists have accumulated a body of clinical experience for the use of the 3 mg/kg dose in clinical practice. This experience is of relevance for the early detection and management of known adverse event profile of ipilimumab which is qualitatively similar in the first and second line clinical setting.[16]

The sponsor agrees with the Delegate and the second round clinical evaluator that the safety profile of 3 mg/kg ipilimumab in pre-treated patients is well known, with a propensity for immune-related adverse events and that treatment with a 3 mg/kg monotherapy dose of ipilimumab in a first line metastatic setting did not provide any new safety signals based on the clinical data submitted with this application.

In response to the Delegates first question on safety from the two observational studies, the sponsor can provide the following information. Safety data continues to be collected in both studies together with survival updates, however, in CA184338 all subjects were off treatment at the last analysis, and in CA184332, 94% were off treatment. Since most immune related events occur during treatment, and only rarely thereafter, the safety data can be considered mature for both studies.

There were no deaths attributed to treatment in either study. In CA184338, there were 142 deaths (52%) of which 127 were due to disease. Accidental death was reported in 3 subjects and 1 patient each died from congestive heart failure/myocardial infarction, pneumonia/sepsis, stroke and pulmonary embolism. The reason for death was unknown in 7 subjects.[19] In CA184332, there were 83 deaths (52.2%) reported at the most recent follow-up, of which 78 deaths were related to melanoma; 1 patient died from acute myocardial infarction, 1 death was not related to melanoma; and the cause of death for 3 patients was unknown.[20]

Sponsor responses to advice sought from the ACPM

Request for post commitment - Study CA184169

The sponsor acknowledges the delegate's question to the committee regarding whether an interim safety analysis for CA184169; 3 mg/kg versus. 10 mg/kg in previously untreated and treated patients should be mandated as a condition of registration given the absence of any randomised, controlled safety data to support the proposed usage. While the sponsor agrees with the Delegates view that the clinical information from this study is of importance, there are some procedural limitations related to maintaining the integrity of this ongoing study that prevents the sponsor from being able to consider an earlier unspecified safety analysis. Reasons for this are outlined below.

- Safety should be considered in the context of efficacy: a previously planned interim analysis was removed from the protocol because enrolment was completed within 5 months instead of the projected 22 months, leading to shorter (less than 18 months) projected follow up at time of interim analysis, which was considered inadequate to assess relative risk/benefit for the 10 mg/kg versus 3 mg/kg dose levels.
- The study is blinded and the sponsor does not have access to unblinded data in order to ensure integrity of the study.
- An independent Data Monitoring Committee (DMC) meets every 6 months and reviews the unblinded data to ensure that subject safety is carefully monitored. Throughout the study, the DMC has recommended continuation of the study with no modification.
- CA184169 randomises previously untreated and previously treated subjects to 3 versus 10 mg/kg ipilimumab. The 3 mg/kg safety data in previously untreated subjects and pre-treated subjects are subsets within the study, and therefore the data

within the untreated subgroup may not provide considerable additional evidence beyond the existing data submitted to TGA. This type of post-hoc analysis can only be performed once all unblinded data is made available to the sponsor following the independent DMC decision to cease the study.

However, the sponsor will commit to the following:

- Inform TGA promptly of DMC decision to amend/terminate the study due to safety concern.
- Submit the final CSR of study CA184169 to the TGA as soon as available. The final analysis will allow a clinically relevant risk-benefit assessment. The actual time of the study completion is event driven, however the last patient last visit is projected to occur in January 2016.

Box warning

The sponsor notes the Delegates request for greater emphasis to warn clinicians of the potential for severe or life threatening adverse events through the introduction of a box warning. The Australian PI currently warns prescribers of the risk of severe or life threatening immune-related adverse reactions, the time period over which these may occur, the need for early detection and management and recommendations for use of immunosuppressive agents. The Australian precaution is identical to that stated in the European SmPC and has been in place since registration of ipilimumab by the TGA. As ipilimumab is now widely used in Australia since registration in July 2011, the introduction of a box warning suggests that a new safety signal has been detected and may unduly alarm clinicians and patients.

Whilst the sponsor is willing to refine this section to create greater emphasis for vigilance in identification and management of these events, it does not consider a box warning to be necessary given that no new safety signals above and beyond those already described in the PI have been detected as part of the evaluation of this application, nor have any new signals been detected through post-marketing surveillance where ipilimumab is now widely used as a first and second line agent.

In the interest of continually improving precautions for use, the sponsor has made suggested changes under PRECAUTIONS in the PI to enhance the existing precautions.

Adjuvant clinical data

The sponsor acknowledges the Delegate's question to the committee in relation to the clinical data from the initial analysis of the adjuvant study CA184029 presented at ASCO 2014.[22] This study is ongoing and aims to compare a 10 mg/kg ipilimumab monotherapy induction dose plus maintenance therapy to best standard of care in the adjuvant setting. The sponsor does not consider the safety data from CA184029 relevant to the requested extension of the indication, for the following reasons:

- Different dose (10 mg/kg versus 3 mg/kg) and schedule (additional maintenance versus 4 induction doses only) in CA184029
- Previously submitted data from pooled Phase II and observational studies do not show higher frequency of irAEs in previously untreated patients with metastatic melanoma.

Given the lack of relevance to the requested indication, and given the data were generated in a very different, unregistered clinical setting, the sponsor does not consider it appropriate to reflect the CA184029 safety observations in the ipilimumab 3 mg/kg advanced melanoma prescribing information. Furthermore, the safety experience should

[22] Eggermont AM, et al. Ipilimumab versus placebo after complete resection of stage III melanoma: initial efficacy and safety results from the EORTC 18071 phase III trial. *J Clin Oncol* 2014; 32:5s, (suppl; abstr LBA9008).

be evaluated in the context of benefit/risk that is, efficacy data should also be considered in the same setting. Therefore, the sponsor proposes that the evaluation of CA184029 safety and efficacy be part of a potential separate submission at a future date.

The sponsor acknowledges that toxicities were higher in the adjuvant setting than in the metastatic setting with the same dose (10 mg/kg) as noted by the Delegate. However, it is unlikely that the lack of prior chemotherapy, or prior treatment in that setting contributed to higher toxicity in a clinically meaningful way. Rather, the following parameters likely explain the higher frequency of irAEs in the adjuvant setting (compared to same dose in advanced melanoma):

- The CA184029 population differs considerably from the proposed indication as all patients who entered had complete surgical resection of their disease prior to ipilimumab (that is, no detectable disease at study entry).
- Given the earlier stage of the disease, the patient population enrolled in CA184029 was considerably younger (median 51 years) than in advanced melanoma studies (median 58 years in CA184024[21] and median 57 years in pooled Phase 2 subjects receiving ipilimumab 10 mg/kg for metastatic disease).
- Both patients in the adjuvant setting, as well as advanced melanoma, received treatment with ipilimumab 10 mg/kg until disease progression/relapse, or unacceptable toxicity. However, while disease progression in the advanced setting occurs within a few months, relapse in the adjuvant setting typically only occurs after a few years. Thus, there are limited reasons other than toxicity to stop treatment for a patient receiving adjuvant ipilimumab, and consequently, most patients in the adjuvant study were treated until they experienced toxicity. InCA184029, at least 1 maintenance dose was received by 198 (42.0%) subjects in the ipilimumab group and at least 7 doses (approximately 1 year of therapy) were received by 136 (28.9%) of subjects in the ipilimumab group.[22] In the pooled Phase 2 population receiving 10 mg/kg ipilimumab for metastatic melanoma, only 10.5%) of subjects (34 of 325) received more than 4 doses.[23]

Sponsor responses to question for the sponsor

1. *For each of the 2 observational studies where patients received 3 mg/kg ipilimumab monotherapy, the sponsor is requested to state the percentage for whom the survival status was unknown at the time of the updated analysis. For what percentage in each study is the safety data complete?*

Response is described in page 60 above. Please also see Tables 16 and 17.

[23] Module 2.7.4, Summary of Clinical Safety. Ipilimumab (BMS-734016/MDX-010). Bristol-Myers Squibb Company, 2012. Document Control No. 930057388.

Table 16: CA184332 Summary of currentness of survival follow-up

	N=157 n (%)
Currentness of Survival Follow-up (Days)[a]	
0[b]	111 (70.7)
1 to 30	4 (2.6)
31 to 60	6 (3.8)
61 to 90	5 (3.2)
91 to 120	1 (0.6)
121 to 150	2 (1.3)
151 to 180	3 (1.9)
180+	25 (15.9)

[a]Time from last known alive date to cutoff date. Cutoff date is 30 September 2013.

[b]Subjects who died, or whose last known alive date was on or after the cutoff date, are classified as having current follow-up (0 days).

Table 17: CA184338 Currentness of survival follow-up

	NUMBER OF SUBJECTS (%) TOTAL (N=273)	
Currentness of Survival Follow-Up (Days) (a)		
0 (b)	142	(52.0)
31 to 60	3	(1.1)
61 to 90	9	(3.3)
91 to 120	10	(3.7)
121 to 150	4	(1.5)
151 to 180	3	(1.1)
181+	102	(37.4)

(a) Time from last known alive date to cutoff date. Cutoff date is the extraction date.
(b) Subjects who died, or whose last known alive date was on or after the cutoff date, are classified as having current follow-up (0 days).

2. *The sponsor is requested to provide updated 2 year survival data for the EAP. If this is not available, the sponsor is requested to provide a justification.*

Final database lock recently occurred for expanded access study CA184045 which included subjects who received previous treatment for metastatic melanoma and did not have any other treatment options. Preliminary final OS data are provided in Appendix E. In general, these data do not show any major difference in relation to previous OS results. A final study report is not yet available.

3. *The sponsor is requested to indicate whether the education program required before being permitted to prescribe when the compassionate access program is still in place. If not, what education is offered to prescribers in its place? Does this prompt prescribers to report adverse events?*

The education program referred to by the Delegate continues to be implemented and the program appropriately encourages health care providers to report adverse events.

Prescribing information

The majority of the changes to the PI requested by the Delegate have been adopted by the sponsor and are outlined in this response. The sponsor accepts the Delegates change to include a statement on the potentially irreversible nature of endocrinopathies. However, there is substantial evidence showing that non-endocrine irAEs resolve in the vast majority of cases with appropriate management.

RMP

The sponsor acknowledges the TGA's recommendation that the RMP is acceptable. The sponsor has agreed to include optic neuritis to the RMP as an identifiable risk and suggestions from the RMP evaluator to be included in the PI have been adopted. The sponsor also agrees to follow up with the TGA on requirements specified in the RMP evaluation report.

Conclusion

Ipilimumab is recognised globally as a major advance in the treatment of patients with unresectable or metastatic melanoma with long-term OS extending beyond 5 years. Regulatory approvals from health authorities with regulatory standards comparable to Australia and endorsement of recommendations by independently peer reviewed guidelines [11,12] have resulted in a global acceptance of the use of ipilimumab 3 mg/kg monotherapy as a standard of care for first line therapy of unresectable or metastatic melanoma.

This accumulation of evidence presented to the TGA now exceeds that provided to other health authorities where regulatory approval has been granted for first line use of ipilimumab.

The clinical benefit of ipilimumab treatment is likely to be greatest in patients who receive it early after diagnosis of metastatic disease due to the kinetics of the anti-tumour response and allows for the greatest probability for completion of all four doses of therapy to ensure the full potential for an immune mediated clinical effect.

The sponsor believes the data presented in this submission supports a favourable benefit-risk balance of ipilimumab (3 mg/kg) in patients with unresectable or metastatic melanoma when administered in the first line metastatic setting.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Yervoy / Winglore containing 200 mg in 40 mL and 50 mg in 10 mL of ipilimumab to have an overall positive benefit–risk profile for the proposed indication;

> *Yervoy, as first line monotherapy, for patients with unresectable or metastatic melanoma.*

In making this recommendation the ACPM

- Noted there is a significant unmet need: Current first line therapies are poor.
- Noted no direct evidence of benefit with the proposed dose or schedule in the proposed population was submitted.

- Was of the view that, although there were significant deficiencies in the evidence provided, it all points to an increased chance of improving overall survival over historical or cross study comparisons.
- Was of the view that the benefit-risk appears positive.

In making this recommendation the ACPM noted the data package was deficient, but the rationale for use in first line is reasonable. As there are no good first line alternatives for those without a BRAF mutation it seems appropriate to allow it but with suitable warnings in place and advice to clinicians, and to patients in particular, on the risk of profound toxicities.

Proposed conditions of registration

The ACPM agreed with the delegate on the proposed conditions of registration and advised on the inclusion of the following:

Submission of the completed CSR for Study CA184169 (the post-marketing study underway comparing 3 mg/kg versus 10 mg/kg) as soon as possible and in the interim, immediate notification of any safety-related modifications or terminations in studies.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI.

Specific advice

The ACPM advised the following in response to the delegate's specific questions on this submission:

1. *Whether an interim safety analysis for CA184169; 3 mg/ kg versus 10 mg/ kg in previously untreated and treated patients – should be mandated as a condition of registration given the absence of any randomised, controlled safety data to support the proposed usage. After an amendment, the sponsor now plans to delay any analyses until all patients have been followed for a minimum of 2 years, and to submit a CSR some 13 months after this. Thus, safety data will also be delayed until this time (safety problems usually occur early).*

While the ACPM was of the view that knowing the safety data may clarify the benefit-risk profile, the committee was sympathetic to the sponsor's arguments on procedural limitations to presenting the data quickly.

The ACPM concurred with the sponsor's commitment to inform the TGA promptly of any DMC decision to amend/terminate the study due to safety concerns and to submit the final report to the TGA as soon as available; projected to occur in January 2016.

2. *Whether a boxed warning is warranted given the deaths, GI perforations, rates of severe and potentially fatal or irreversible immune-related AEs.*

The ACPM noted that both the USA and Canadian PIs have a black box. The sponsor's argument that that as there was no new safety signal this might unduly "alarm clinicians and patients" was not accepted. The safety signals already acknowledged have been reinforced. Those treating melanoma are well aware of the toxicities, which are profound. The ACPM advised it agreed with the Delegate that a black box is required given the severity and irreversibility of the AEs. In addition, the ACPM agreed with the sponsor on the need for improving the precautions section in the PI.

3. *How best to reflect the safety signals from the adjuvant study to inform regarding the risk in previously untreated patients, given no other randomised safety.*

While the safety data from the adjuvant study is difficult to interpret for this indication the ACPM agreed the patient group more closely resembles the targeted group, but the

treatment dose is still higher, and treatment duration longer, so it is not easy to utilise this information.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Yervoy / Winglore ipilimumab (rch) 200 mg in 40 mL and 50 mg in 10 mL concentrate solution for IV infusion[, indicated for:

> *Yervoy/Winglore, as monotherapy, is indicated for the treatment of patients with unresectable or metastatic melanoma.*

Specific conditions of registration applying to these goods

- The Yervoy/Winglore EU-RMP Version 8.2 (data lock point 18 September 2012) with Australian-specific Annex version dated 29 November 2013, and any subsequent revisions, as agreed with TGA will be implemented in Australia.
- Submission of the completed CSR for Study CAI84169 (the post-marketing study underway comparing 3 mg/kg versus 10 mg/kg) as soon as possible and, in the interim, immediate notification of any safety-related modifications or terminations in studies.

Attachment 1. Product Information

The PI for Yervoy approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>. The PI for Winglore is identical except for the product name.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au