Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for brentuximab vedotin

Proprietary Product Name: Adcetris

Sponsor: Takeda Pharmaceuticals Australia Pty Ltd

May 2014

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 <http://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 abbreviations

Abbreviation	Meaning
ABVD	Combination of doxorubicin, bleomycin, vinblastine and dacarbazine
ACPM	Advisory Committee on Prescription Medicines
ADA	Anti-drug antibodies
ADC	Antibody drug conjugate
AE	Adverse event
ALCL	Anaplastic large cell lymphoma
ALK	Anaplastic lymphoma kinase
AlloSCT	Allogeneic hematopoietic stem cell transplantation
ALT	Alanine transaminase
ARTG	Australian Register of Therapeutic Goods
ASCT	Autologous stem cell transplant
AST	Aspartate aminotransferase
AUC	Area under the curve
ATA	Anti-tumour antibody
$AUC_{0\text{-}21days}$	Area under the curve during 21 days
$AUC_{0\text{-}\infty}$	the area under the plasma concentration time curve from time zero to the last measurable time point
AVD	Combination of doxorubicin, vinblastine and dacarbazine
BCRP	Breast cancer resistant protein transporter
BEACOPP	Combination of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone
BEACOPP	Combination of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone
BrECADD	Combination of brentuximab vedotin, etoposide, Adriamycin, cyclophosphamide, dacarbazine and dexamethasone.
BrECAPP	Combination of brentuximab vedotin, etoposide, Adriamycin, cyclophosphamide, procarbazine and prednisone.

Abbreviation	Meaning
CCRIS	Chemical carcinogenesis research information system
CHOP	Combination of cyclophosphamide, doxorubicin, vincristine, and prednisone
CH-P	Combination of cyclophosphamide, doxorubicin and prednisone
Cmax	Clinical maximum concentration
CMI	Consumer Medicines Information
CNS	Central nervous system
CR	Complete response
CrCl	Creatinine clearance
CSR	Clinical study report
CT	X-ray computed tomography
CYP450	Cytochrome P450
DDI	Drug to drug interaction
DHAP	Combination of dexamethasone, cisplatin and high dose cytarabine
DLP	Data lock point
DP	Drug Product
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FDG	Fluorodeoxyglucose
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transpeptidase
GLP	Good Laboratory Practice
GVD	Combination of gemcitabine, vinorelbine and liposomal doxorubicin

Abbreviation	Meaning
GMR	Geometric mean ratio
HL	Hodgkin's lymphoma
IC_{50}	Inhibitory Concentration 50
ICE	Ifosfamide, carboplatin and etoposide.
ICH	The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IgG1	Immunoglobulin G1
IP	Intraperitoneal
IRF	Independent review facility
ITT	Intention to treat
IV	Intravenous
KD values	The equilibrium dissociation constant between the antibody and its antigen
K_I	Concentration at 50% K_{inact}
K_{inact}	Inactivation rate
K_{inact}/K_I	Cytochrome P450 time dependent inhibition
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activites
MMAE	Monomethyl auristatin
MRP2	Multidrug resistance associated protein 2
NCCN	National Comprehensive Cancer Network
NK	Natural killer
NR	Not reportable
ORR	Overall response rate
OS	Overall survival
PBS	Phosphate buffered saline
pcALCL	Primary cutaneous anaplastic large cell lymphoma

Abbreviation	Meaning
PD	Pharmacodynamic
PET	Positron emission tomography
PFS	Progression free survival
P-gp	P-glycoprotein
PI	Product Information
PK	Pharmacokinetic
PR	Partial remission
PSC	Pharmaceutical Subcommittee
PSUR	Periodic safety update report
QTc	corrected Q-T interval
RMP	Risk Management Plan
SAE	Serious adverse event
sALCL	Systemic anaplastic large cell lymphoma
SC	Subcutaneous
SD	Stable disease
SGN-30	An unconjugated anti-CD30 antibody
SGN-35	Brentuximab vedotin
SOCs	System organ classes
TEAE	Treatment emergent adverse event
$T_{1/2}$	Half life
TGA	Therapeutic Goods Administration
Tmax	Time to maximum concentration
US	United States
CMV	cytomegalovirus
URTI	Upper respiratory tract infection
TEN	Toxic epidermal necrolysis

Abbreviation	Meaning
PML	Progressive multifocal leukoencephalopathy
SJS	Stevens Johnson Syndrome
PN	Peripheral neuropathy
HDC	High dose chemotherapy

I. Introduction to product submission

Submission details

Type of submission:	New Chemical Entity
Decision:	Approved
Date of decision:	19 December 2013
Active ingredient:	Brentuximab vedotin
Product name:	Adcetris
Sponsor's name and address:	Takeda Pharmaceuticals Australia Pty Ltd 2-4 Lyonpark Road Macquarie Park NSW 2113
Dose form:	Powder for injection
Strength:	50 mg
Container:	Vial
Pack size:	One
Approved therapeutic use:	*Treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL):* • *Following autologous stem cell transplant (ASCT) or* • *Following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option* *Treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL).*
Route of administration:	Intravenous infusion
Dosage:	1.8 mg per kg intravenous infusion over 30 minutes every 3 weeks
ARTG number :	203372

Product background

This AusPAR describes the application by the sponsor to register Adcetris for the following two indications:

1. *The treatment of adult patients with relapsed or refractory Hodgkin's lymphoma (HL) either following autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option.*

2. *Treatment of adult patients with relapsed or refractory or systemic anaplastic large cell lymphoma (sALCL).*

Adcetris is a CD30 directed antibody drug conjugate (ADC) consisting of three components,

- The chimeric Immunoglobulin G1 (IgG1) antibody cAC10, specific for human CD30.
- The potent micro-tubule disrupting agent monomethyl auristatin E (MMAE), and
- A protease cleavable linker that covalently attaches MMAE to cAC10.

Non-clinical data suggest that the biological activity of Adcetris results from a multi-step process. Binding of the ADC to CD30 on the cell surface initiates internalisation of the ADC CD30 complex which then traffics to the lysosomal compartment. Within the cell a single defined active species MMAE is released by proteolytic cleavage. Binding of MMAE to tubulin disrupts the micro-tubule network within the cell inducing cell cycle arrest and results in apoptotic death of the CD30 expressing tumour cell.

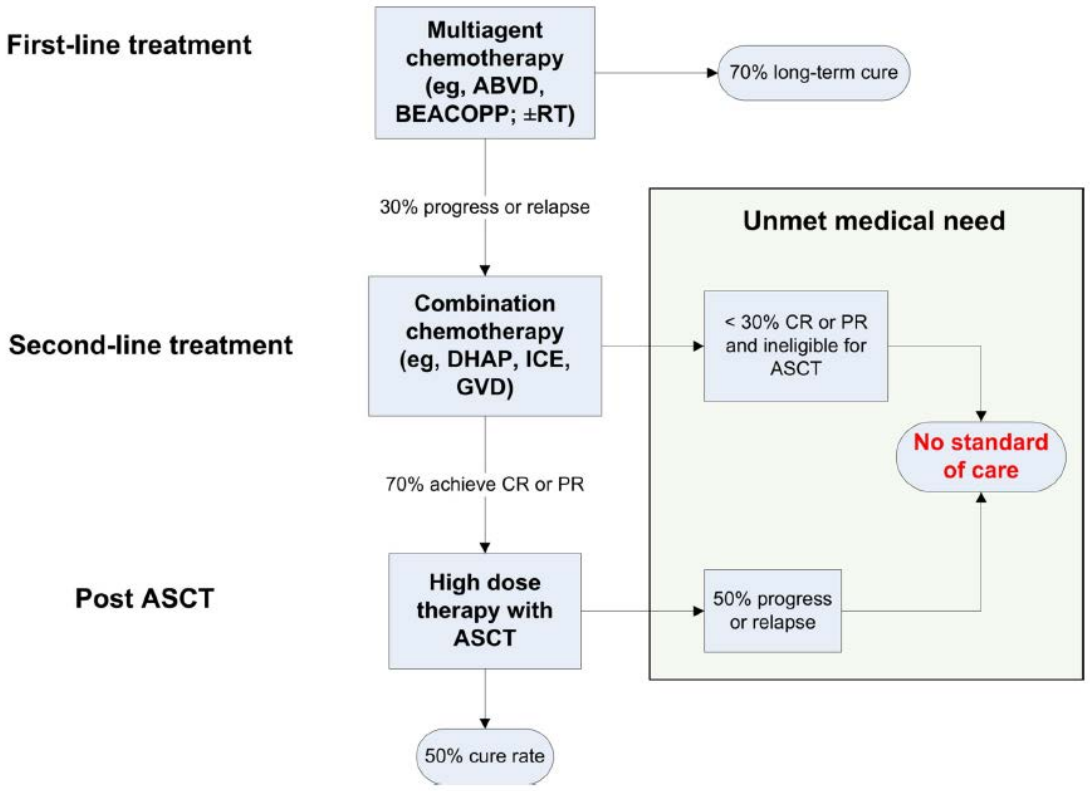
It is proposed to market Adcetris as a 50 mg powder for intravenous injection.

Hodgkin Lymphoma (HL)

HL is histopathologically defined by presence of Reed-Sternberg cells on a background of inflammatory cells. The characteristic surface antigen on Reed-Sternberg cells is CD30. (The bulk of the HL tumour mass does not express CD30.) National Comprehensive Cancer Network (NCCN) guidelines note that classical HL has this picture. (Lymphocyte-predominant HL is characterised by lymphocytic and histiocytic cells; it has a different natural history and response to therapy; and it is often CD30 negative.) The sponsor provides an HL treatment scheme [1], apparently focusing on cHL, see Figure 1.

[1] ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; BEACOPP = bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; ICE = ifosfamide, carboplatin, etoposide; DHAP = dexamethasone, cisplatin, high dose cytarabine; GVD = gemcitabine, vinorelbine, liposomal doxorubicin

Figure 1. Treatment scheme

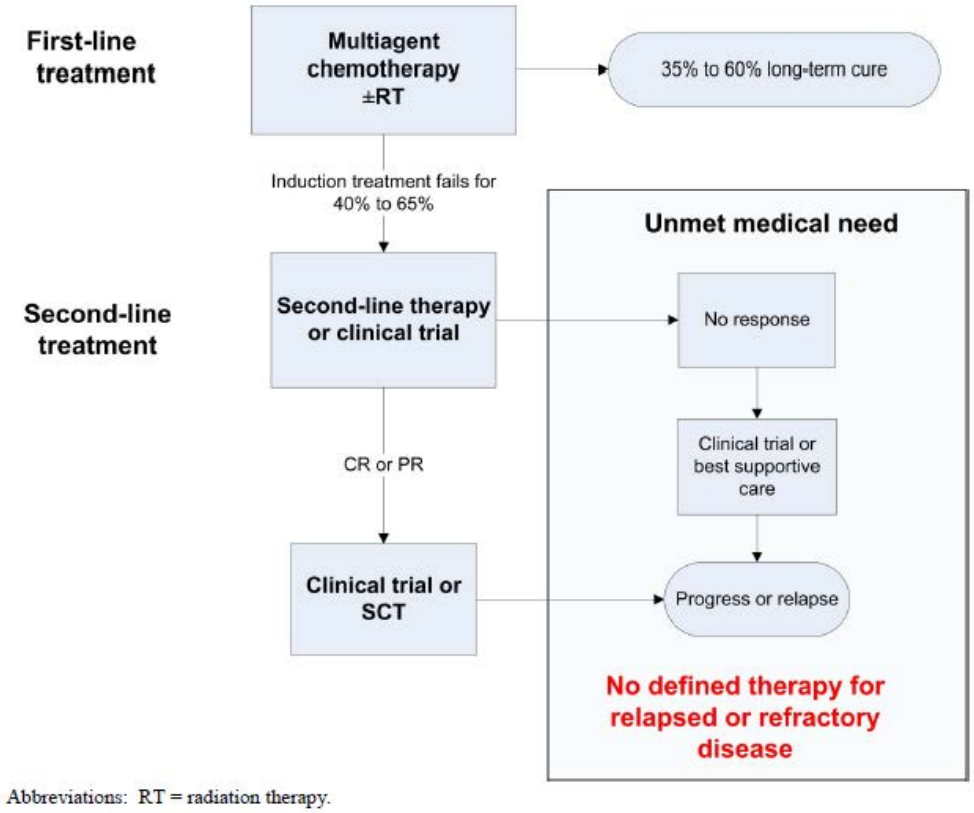


NCCN guidelines (Version 2, 2013; MS-23 to MS-26) distinguish between classical HL and lymphocyte-predominant HL in recommendations for refractory and relapsed disease.

Systemic anaplastic large cell lymphoma (sALCL)

The sponsor notes anaplastic large cell lymphoma (ALCL)s '*characterised by large, pleomorphic lymphoid cells expressing CD30,'* and that '*the uniform, strong expression of CD30 throughout the disease continuum differentiates ALCL from other forms of peripheral T cell lymphoma.'* ALCL can be systemic or primary cutaneous. Anaplastic lymphoma kinase (ALK) status is prognostic in sALCL (ALK positive disease is associated with better prognosis; it is found in 50 to 80% of cases).

Figure 2. Sponsor's summary of current treatment

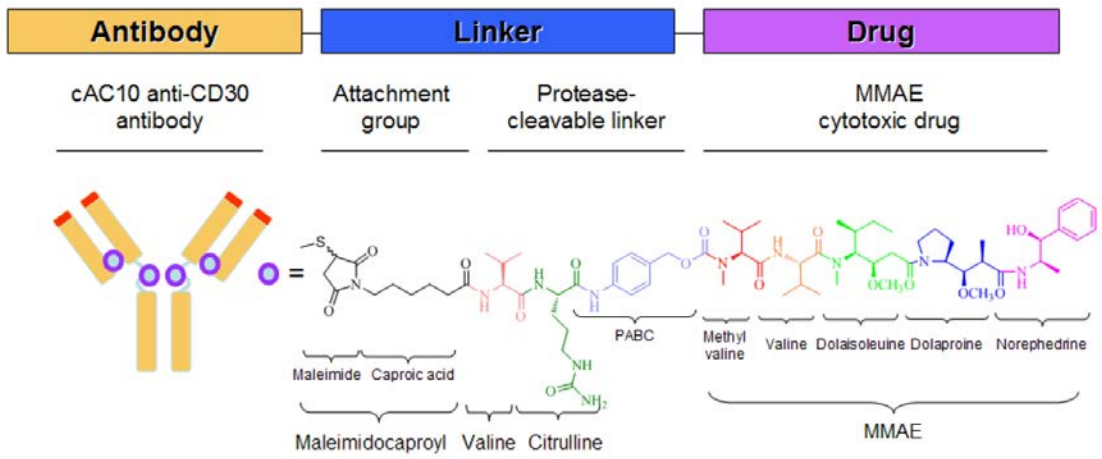


Abbreviations: RT = radiation therapy.

Targets and mechanism of action

Adcetris is a 153 kDa, CD30-directed antibody-drug conjugate with three components and is also referred to in literature as SGN-35 (Seattle Genetics is the US sponsor).

Figure 3.



Adcetris has been designated an orphan drug in Australia for relapsed or refractory HL and sALCL, on 18 September 2012.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 20 December 2013.

At the time the TGA considered this application, a similar application had been lodged in the following countries:

- United States (US): Adcetris was given accelerated approval in the US on 19 August 2011 and its indications are as follows (based on label version approved 19 August 2013):
  - Hodgkin Lymphoma
    - *Adcetris (brentuximab vedotin) is indicated for treatment of patients with Hodgkin lymphoma (HL) after failure of autologous stem cell transplant (ASCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates.*
  - Systemic Anaplastic Large Cell Lymphoma
    - *Adcetris is indicated for treatment of patients with systemic anaplastic large cell lymphoma (sALCL) after failure of at least one prior multi-agent chemotherapy regimen.*
- European Union: Adcetris was given conditional approval on 25 October 2012 as follows:
  - *Adcetris is indicated for the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL):*
    - *following autologous stem-cell transplant (ASCT) or;*
    - *following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option.*
  - *Adcetris is indicated for the treatment of adult patients with relapsed or refractory systemic anaplastic large-cell lymphoma (sALCL).*

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

II. Quality findings

Drug substance (active ingredient)

Brentuximab vedotin consists of cAC10 conjugated to SGD-1006 via thioether bonds. Each antibody molecule has on average, two of its interchain disulfides reduced and the resulting cysteine residues aklylated with SGD-1006 leading to a molar ratio (MR_D) of four drugs per antibody. This leaves, on average, two interchain disulfides per molecule intact. One drug conjugation site is located in the light chain and three conjugation sites are located in the heavy chain, resulting in many active forms with up to eight possible conjugation sites per antibody.

Drug product

Brentuximab vedotin (SGN-35) Drug Product (DP) is a sterile, preservative free, white to off-white lyophilised cake or powder supplied in a single use container. Prior to administration, SGN-35 DP is reconstituted with 10.5 mL of sterile Water for Injection

resulting in a clear to slightly opalescent, colourless solution, containing 5 mg/mL SGN-35, 20 mM sodium citrate, 6.3% (weight per volume (w/v)) trehalose, 0.2 mg/mL polysorbate 80, pH 6.6. For administration, the reconstituted solution is added to an intravenous infusion bag containing infusion solution.

Each vial contains an overfill relative to the nominal content (50 mg per vial) to ensure that the labelled quantity can be withdrawn from the vial. The product vial is reconstituted with 10.5 mL of water for injection to achieve reconstituted SGN-35 at 5 mg/mL. There are no overages included in SGN-35 DP.

Biopharmaceutics

This product is an intravenous monoclonal antibody and Biopharmaceutic data are not usually required to be evaluated.

Advisory committee considerations

There are minor labelling and packaging documentation issues which are being addressed, and include, incorrect sponsor address on PI, incorrect website address on PI, reference on PI to indicate the expiry date and "made in US" claim on labels.

The Pharmaceutical Subcommittee (PSC) was also requested to provide general advice, please refer to the Delegate's Overview for discussion.

Quality summary and conclusions

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

III. Nonclinical findings

Introduction

The overall quality of the submitted nonclinical dossier was high, with all pivotal toxicity studies conducted under Good Laboratory Practice (GLP) conditions using the proposed clinical route (Intravenous (IV)). Studies were in general accordance with the relevant guidelines (The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) S9, Nonclinical evaluation for anticancer pharmaceuticals and ICH S6(R1), Preclinical safety evaluation of biotechnology-derived pharmaceuticals).

Pharmacology

Primary pharmacology

Rationale and mechanism of action

Brentuximab vedotin is an anti-CD30 antibody (cAC10) conjugated via a protease-susceptible linker (composed of maleimide, caproic acid, valine, citrulline and p-aminobenzylcarbamate) to the anti-microtubule agent, monomethyl auristatin E (MMAE). The molar ratio of MMAE to antibody is 4. CD30 is a transmembrane protein that belongs

to the tumour necrosis factor receptor superfamily. The expression of CD30 is largely restricted to activated T cells, B cells and natural killer (NK) cells, but has also been found to be expressed on ALCL cells, Reed-Sternberg cells in Hodgkin lymphoma as well as cells involved in other haematological malignancies.[2] Following binding to CD30 expressing cells, brentuximab vedotin is intended to be internalised and transported to lysosomes, where the MMAE component is released and binds to tubulin, leading to cell cycle arrest and apoptosis. While some cytotoxic activity may come from the monoclonal antibody component, the majority of the activity is likely to come from MMAE.

In vitro studies

Brentuximab vedotin bound to several human CD30 positive lymphoma cell lines (HL, ALCL and Epstein-Barr virus large cell lymphoma cell lines) and activated human lymphocytes. The binding kinetics of brentuximab vedotin were similar to those seen with the unconjugated antibody (cAC10); the equilibrium dissociation constant between the antibody and its antigen (KD values) to a CD30-positive ALCL cell line were 1.4 to 2.6 nM. The binding kinetics of both cAC10 and brentuximab vedotin to activated human and Cynomolgus monkey lymphocytes were similar (KD circa 0.2 nM). There was no significant binding of brentuximab vedotin or cAC10 to rat or mouse CD30 (using a murine CD30-positive cell line and activated rat and mouse T cells) and no significant binding to CD30-negative human lymphoma cell lines.

Using immunofluorescence imaging, the internalisation of brentuximab vedotin in a CD30-positive human HL cell line was demonstrated at 4 hours and increased up to 24 hours. Co-localisation with a lysosomal marker (Lamp-1) was demonstrated. MMAE release from brentuximab vedotin was demonstrated in CD30-positive cells. This release was also demonstrated with purified lysosomal protease cathepsin B, as well as lysosomal fractions from a human ALCL cell line. Using protease inhibitors and temperature reduction, the release of MMAE was suggested to be enzymatic. In an in vitro tubulin assay, MMAE inhibited microtubule polymerisation (Inhibitory Concentration 50 (IC_{50}) 1 μM), comparable with vinblastine (IC_{50} 1.4 μM). Exposure of a human CD30-positive cell line to brentuximab vedotin disrupted the microtubule network. Brentuximab vedotin induced G2/M phase cell cycle arrest and cytotoxicity of human CD30-positive HL and ALCL cell lines with IC_{50} values ranging from 0.46 to 18.7 ng/mL. There was no induction of cell cycle arrest or cytotoxicity with CD30-negative cells. In contrast, MMAE induced cell cycle arrest and cytotoxicity of all cell lines, regardless of the CD30 expression level. The data demonstrate that brentuximab vedotin targets CD30-positive cells, specifically. Brentuximab vedotin induced antibody-dependent cell phagocytosis of CD30-positive cells, but there was minimal antibody-dependent cellular cytotoxicity and no evidence of complement-dependent cytotoxicity in adequately conducted assays.

Together, the data indicate that Cynomolgus monkeys are good animal models to assess the toxicity of brentuximab vedotin based on pharmacological considerations. The antibody component of brentuximab vedotin is not pharmacologically-active in rodents, but these species should be adequate animal models to assess the toxicity of MMAE. Once brentuximab vedotin is bound to CD30-positive cells, MMAE is released in the lysosomal fraction. The primary cytotoxic action is mediated by the tubulin inhibitory activity of the MMAE component of brentuximab vedotin. Minimal cytotoxic activity would be mediated by the antibody component.

One metabolite of MMAE (keto-Nor(C8)-MMAE) had equipotent cytotoxic activity to MMAE, while two other metabolites (N-demethyl-Val(C7)-MMAE and O-demethyl-Dap(C4)-MMAE) were less cytotoxic (greater than 2000 and 10 to 150 times, respectively). Given the limited metabolism of MMAE and the (generally) lower cytotoxic activity of these

[2] Deutsch, Y.E., T. Tadmor, E.R. Podack and J.D. Rosenblatt. (2011) CD30: an important new target in hematologic malignancies. Leukem. Lymphom. 52: 1641–1654.

metabolites, they are not expected to significantly contribute to the anti-tumour activity of brentuximab vedotin.

In vivo studies

The anti-tumour activity of brentuximab vedotin, MMAE, cAC10 and/or cAC10+MMAE was examined in mice bearing human CD30-positive xenografts of HL and ALCL. Brentuximab vedotin (greater than or equal to 2 mg/kg (approximately 52 nmol/kg MMAE[3]) by intraperitoneal (IP) injection q4d times 3 or 4) significantly delayed tumour growth in mice bearing subcutaneous (SC) implants of HL cells. Complete and durable tumour regression was seen, with the majority of mice having no detectable tumours at the end of the study. Mice that received 0.25 mg/kg (350 nmol/kg) IV MMAE q4d times 3 had a slight delay in tumour growth, but still developed large tumours.

Delayed tumour growth with a complete and durable response was seen in the majority of mice containing an SC implant of ALCL cells that received 0.5 mg/kg (approximately 13.2 nmol/kg MMAE[3]) IV q4d times 4 brentuximab vedotin. No effect was seen with MMAE (0.01 mg/kg (13.9 nmol/kg) IV q4d times 4) or cAC10 (0.5 mg/kg IV q4d times 4). A slight retardation of tumour growth was seen with cAC10+MMAE at 0.5+0.01 mg/kg q4d times 4, but no animals showed a complete or durable response. In a disseminated form of the disease, a dose-related increase in survival was observed with brentuximab vedotin; significant at greater than or equal to 1 mg/kg IV q4d times 4 (mean survival: more than 89 days), with all mice that received 3 mg/kg still alive at the end of the study (Day 106). A slight increase in mean survival (54 days compared with 36 days for untreated control) was seen with cAC10+MMAE at 3+0.06 mg/kg IV q4d times 4 (corresponding to 83.9 nmol/kg MMAE) but it was less effective than brentuximab vedotin (at greater than or equal to 1 mg/kg (approximately 26.4 nmol/kg MMAE)). These studies demonstrate that brentuximab vedotin had greater anti-tumour activity (on a molar basis) than MMAE alone, cAC10 alone or the combination of cAC10 and MMAE. The in vivo studies support the proposed clinical use of brentuximab vedotin in patients with CD30-positive HL and sALCL.

Secondary pharmacodynamics

Both brentuximab vedotin and cAC10 were assessed for cross-reactivity to human tissues. No specific binding was detected with cAC10. However, in a second study with brentuximab vedotin, some binding to mononuclear cells, haematopoietic precursor cells, spindloid cells, oviduct and bronchial epithelium and keratin squames/debris was seen. In isolated samples, binding to kidney tubules, lens protein and thyroid colloid was evident. In a screen against monkey tissues, cAC10 was found to bind specifically to thyroid epithelial cells, but no other tissues. Brentuximab vedotin did not bind to rat liver samples. While brentuximab vedotin binds fairly specifically to CD30-positive human tissues, the significant level of circulating MMAE, which is cytotoxic regardless of CD30 expression levels, indicates a potential for off-target effects due to this drug-related component.

Safety pharmacology

Safety pharmacology studies included an in vitro study assessing the effect of MMAE on hERG K^+ tail current and an in vivo study assessing the effect of brentuximab vedotin on the cardiovascular, respiratory and central nervous systems of Cynomolgus monkeys. Both studies were conducted under GLP conditions. Some inhibition (24%) of hERG K^+ tail current was seen at the highest tested MMAE concentration (100 µM). No significant inhibition (less than 11%) was seen at 10 µM (1170 times the clinical maximum concentration (C_{max})). No adverse effects were seen on respiratory, cardiovascular or

[3] Brentuximab vedotin has 4 moles MMAE/mole antibody.

neurological parameters in Cynomolgus monkeys given less than 3 mg/kg IV brentuximab vedotin over a 1 hour infusion (estimated C_{max} 80.4 µg/mL for brentuximab vedotin (2 times the clinical C_{max}) and 35 ng/mL for MMAE (6 times the clinical C_{max})[4]). Overall, adverse effects on the cardiovascular, respiratory and central nervous systems during clinical use are not predicted from the animal data.

Pharmacokinetics

Following IV administration, the elimination half-life of brentuximab vedotin was long (rats, 8 to 15 days ; Cynomolgus monkeys, 2 to 3 days; humans, 6.7 days). The half-life was shorter in monkeys in which anti-drug antibodies (ADAs) had been generated. Following administration of brentuximab vedotin to rats, monkeys and humans, the maximum concentrations of MMAE were seen 1 to 3 days post-dose, while the apparent half life ($t_{1/2}$) in monkeys and humans were generally similar to or slightly shorter than those seen with brentuximab vedotin. On a molar basis, the exposure to MMAE was less than 0.1% and 10% of brentuximab vedotin in monkeys and humans, respectively. Exposure to total antibody was higher than brentuximab vedotin alone in all species (up to 2 times higher). Exposures to brentuximab vedotin and total antibody were similar after the first dose and fourth weekly dose of brentuximab vedotin to monkeys in which ADAs had not been induced. Lower exposures to brentuximab vedotin and total antibody were seen with repeated doses to monkeys with ADAs.

In the pivotal 6 month repeat-dose toxicity study in monkeys, exposures to MMAE in animals with ADAs were 20 to 50 times higher following the eighth dose compared with the first dose, while no difference was seen in animals lacking ADAs (based on data from one monkey without detectable ADA), suggesting ADA clearance of brentuximab vedotin is associated with higher MMAE levels.

In humans, following dosing every 3 weeks, minimal to no accumulation of brentuximab vedotin was observed and exposures to the test item did not decrease with subsequent doses, while exposure to MMAE decreased with repeated doses.

Accumulation of brentuximab vedotin was not assessed in rats. Consistent with the long half-life, clearance of brentuximab vedotin and total antibody was low in all species. Following IV administration, the half-life of the unconjugated antibody (cAC10) was longer than brentuximab vedotin in monkeys (6 to 16 days). In rats, the elimination half-life of MMAE was much shorter following IV administration with MMAE alone (approximately 5 hours) compared with following brentuximab vedotin, suggesting the pharmacokinetics of MMAE were governed by the rate of release of MMAE from brentuximab vedotin. Some accumulation was evident following once weekly dosing with MMAE to rats. No apparent sex differences in plasma kinetics were seen in rats following MMAE administration or in monkeys following brentuximab vedotin or MMAE administration.

There were clear species differences in plasma protein binding by MMAE with binding similar in the plasma of rats and humans (72 to 82%) and much lower in monkeys (18%). There was no evidence of a concentration relationship with binding in the plasma of rats or monkeys, but there was a small concentration-related increase in binding in human plasma (68 to 82% over 1 to 100 nM). The bound fraction in humans at the C_{max} is estimated to be approximately 75%. Typical for an antibody, the volume of distribution of brentuximab vedotin was lower than total body water in rats, monkeys and humans, suggesting limited extravascular distribution. In rats, the volume of distribution of MMAE was greater than total body water. Consistent with this, tissue distribution of radioactivity was rapid and wide following IV administration of radiolabelled MMAE, with most tissue

[4] Based on data from Study SNBL-163-16 (11 week repeat-dose toxicity study).

to plasma C_{max} ratios of radioactivity of 20 to 30. Aside from organs involved in excretion (including the liver and kidney), high tissue levels of radioactivity were seen in the adrenal gland, anterior pituitary gland, thyroid and lungs. There was some evidence of retention of radioactivity in the melanin-containing uveal tract. There was limited penetration of the blood-brain barrier. The findings in the tissue distribution study, however, should be considered with caution, as the extent of ^{3}H-exchange in tissue is unknown, while considerable ^{3}H-exchange was seen in plasma.

No specialised studies were conducted to assess the metabolism of brentuximab vedotin in animals. However, in vitro studies were conducted to assess the stability of brentuximab vedotin in the plasma of rats, monkeys and humans, the metabolism of MMAE in human liver microsomes, in microsomes expressing human Cytochrome P450 (CYP450) enzymes and in rat, monkey and human hepatocytes, and to characterise the metabolites of MMAE in the excreta of rats and humans. Following internalisation into CD30-positive cells, MMAE is released from brentuximab vedotin in the lysosomal compartment. In vitro studies suggested a major role of cysteine proteases, in particular cathepsin B, in the release of MMAE from brentuximab vedotin. Brentuximab vedotin was relatively stable in rat, monkey and human plasma with less than or equal to 2% of the maximum theoretical amount of MMAE released over 21 days. The highest level was in rat plasma (2% compared with 0.5% in human and monkey plasma) and higher than in phosphate buffered saline (PBS), suggesting some proteolytic cleavage occurs in the absence of CD30 binding and internalisation. Exposures to MMAE were significantly higher in monkeys with ADAs, indicating ADA-associated clearance of brentuximab vedotin generates release of MMAE.

Following proteolytic cleavage of MMAE from brentuximab vedotin, the antibody component is likely to undergo further proteolytic degradation, as would be expected for this type of molecule. MMAE undergoes further degradation, followed by elimination. The major radiolabelled drug-related material in the excreta of rats and humans was unchanged MMAE (greater than or equal to 75%) suggesting MMAE undergoes limited metabolism. A total of 13 MMAE-related metabolites were identified across in vitro and in vivo studies. Nine metabolites were identified in rat samples, 12 in monkey samples and 10 in human samples. Only one human-specific metabolite (an O-demethylated, oxidised metabolite) was identified in urine and faeces. Given the low level of metabolism of MMAE, and the low level of this metabolite compared with total parent drug (brentuximab vedotin), this is not expected to limit the utility of rats or monkeys as animal models for toxicity. The primary metabolic pathway of MMAE involved N- and O-demethylation, dehydrogenation, amide hydrolysis and oxidation. In hepatocyte incubations, O-demethylation and hydroxylation products were major metabolites in rats, monkeys and humans. One oxidation product had similar cytotoxic activity to MMAE, while the N- and O-demethylation products had lower activity. Incubations with microsomes from cells expressing recombinant human CYP450 enzymes indicated a major role of CYP3A4 in the O-demethylation, N-demethylation and dehydrogenation of MMAE with a minor contribution of CYP2D6 in the N-demethylation reaction.

Mass balance studies were conducted in rats following IV dosing with ^{3}H-MMAE and (^{3}H-MMAE)brentuximab vedotin and in human subjects following IV dosing with brentuximab vedotin. Excretion of drug-related material in both species was primarily via the faeces (89 to 102% in rats and 72% in humans). Intact MMAE was the dominant drug-related compound in both rats and humans, constituting greater than or equal to 75% of the MMAE-related compounds excreted. In rats, greater radioactivity was excreted in a shorter period following MMAE dosing compared with brentuximab vedotin dosing with 90 to 95% excreted in 48 hours compared with 50% excreted in 48 hours following

brentuximab vedotin dosing. This is consistent with the slow formation of MMAE and slower clearance of the antibody-drug complex.

Overall, the pharmacokinetics of brentuximab vedotin was qualitatively similar in rats, monkeys and humans, thus supporting the use of the chosen species in the toxicity studies.

Pharmacokinetic drug interactions

Potential pharmacokinetic drug interactions were considered for the MMAE component of brentuximab vedotin. The antibody component is not expected to be involved in any pharmacokinetic drug interactions. MMAE (less than or equal to 10 μM; 1170 times the clinical C_{max} [5]) did not induce CYP1A2, 2B6, 2C8, 2C9, 2C19 or 3A4/5 activities in human hepatocytes. However, a non-concentration-related decrease in the activity of all tested CYP450s was observed (by 32 to 70%), even at the lowest concentration tested (0.1 μM; 14 times the clinical C_{max}). The mechanism and significance of this reduction is unknown but it was not associated with a reduction in cell viability. MMAE was a direct inhibitor (with midazolam but not testosterone as a substrate) (IC_{50} 10 μM; 1170 times the clinical C_{max}) and a time-dependent inhibitor of CYP3A4/5 (both substrates) (Inactivation rate (k_{inact}) 0.1 min^{-1}, concentration at 50% k_{inact} (K_I) 1.12 μM). Based on the relatively high Cytochrome P450 Time Dependent Inhibition (k_{inact}/K_I) compared with unbound plasma concentrations of MMAE, this inhibitory activity is not expected to be clinically relevant. There was little to no direct inhibition of CYP1A2, 2B6, 2C8, 2C9, 2C19 or 2D6 (IC_{50} greater than 100 μM; approximately 12,000 times the clinical C_{max}). Taken together, based solely on data with MMAE, brentuximab vedotin is not expected to alter the pharmacokinetics of co-administered drugs through interactions with CYP450 enzymes.

The metabolism of MMAE, the cytotoxic component of brentuximab vedotin, involves primarily CYP3A4/5. Inhibitors/inducers of CYP3A4/5 may alter MMAE exposures, which, in the case of an inhibitor, could result in more significant side effects. Pharmacokinetic drug interactions involving the linker components have not been assessed. Given the anticipated low circulating level of the linker components, this is not expected to be a concern.

MMAE was not a substrate for breast cancer resistant protein transporter (BCRP), multidrug resistance-associated protein 2 (MRP2), organic anion-transporting polypeptides (hOATP1B1, hOATP1B3,) or octamer transcription factors (hOCT2 or hOAT1). MMAE was a P-glycoprotein substrate and a probable P-glycoprotein inhibitor (IC_{50} approximately 19 μM (2200 times the clinical C_{max}) in the vesicular transport assay). Given the low circulating levels of MMAE, the P-glycoprotein inhibitory activity is not expected to be clinically-relevant. As MMAE primarily undergoes hepatobiliary excretion, enterohepatic recirculation and greater systemic exposure to this cytotoxic compound (and therefore greater toxicity) may be seen if brentuximab vedotin is co-administered with a P-glycoprotein inhibitor. The proposed Product Information document for Adcetris states that exposure to MMAE increased by approximately 73% in patients when brentuximab vedotin was co-administered with the CYP3A4 and P-glycoprotein inhibitor, ketoconazole. Co-administration of brentuximab vedotin with a P-glycoprotein inhibitor may also increase the exposure of the central nervous system (CNS) to MMAE, leading to a greater risk for neurotoxicity.

[5] Based on a C_{max} of 6.1 ng/mL (8.5 nM)

Toxicology

Acute toxicity

Single-dose toxicity studies were conducted in rats and Cynomolgus monkeys following IV administration of brentuximab vedotin or MMAE. None of the studies were GLP-compliant and the conduct of the studies had some limitations according to the criteria described in the EU note for guidance on single-dose toxicity studies (3BS1a). The observation period in the rat studies (4 to 14 days) is considered rather short, given the half-life of brentuximab vedotin in this species (8 to 15 days), while the observation period in the monkey studies is considered adequate (63 days). However, no post-mortem analyses were conducted in the monkey studies, limiting the usefulness of these studies. These limitations are not expected to affect the interpretation of the toxicity profile of brentuximab vedotin and MMAE, given the collective findings in these studies and those in the repeat-dose toxicity studies.

No deaths were seen in animals that received brentuximab vedotin but the tested doses were lower than the proposed clinical dose adjusted for body surface area [6] or only 1.5 to 5 times the clinical dose on a mg/kg basis. Deaths were noted in some animals that received MMAE (200 µg/kg in rats and 116 µg/kg in monkeys). The maximum non-lethal doses were 100 µg/kg IV MMAE and 10 mg/kg IV brentuximab vedotin in rats and 3 mg/kg IV brentuximab vedotin in monkeys.

A maximum non-lethal dose of MMAE was not determined in monkeys. Clinical signs included soft faeces and white discharge from the penis in rats that received MMAE, hunched posture, inappetance and emesis in monkeys that received MMAE and hunched posture in monkeys that received brentuximab vedotin. In general, the toxicity findings were similar with both test items in both species, with the liver (elevated enzymes with evidence of tissue damage), gastrointestinal tract (faecal changes, emesis and single cell necrosis seen during post-mortem analyses) and bone marrow (with subsequent haematological changes and secondary effects on lymphoid organs) as target organs for toxicity. ADAs were seen in 5 out of 6 monkeys that received brentuximab vedotin. As the maximum non-lethal dose with MMAE in rats was less than the maximum expected from brentuximab vedotin administered clinically [7] and toxic signs were evident at subclinical doses (based on body surface area)of both brentuximab vedotin and MMAE to rats and monkeys, both MMAE and brentuximab vedotin are considered to have a high order of toxicity.

Repeat-dose toxicity

Repeat-dose toxicity studies were conducted with brentuximab vedotin in rats (up to 4 weeks) and Cynomolgus monkeys (up to 6 months). Based on both pharmacological and pharmacokinetic parameters, monkeys are the most appropriate species to assess the toxicity of brentuximab vedotin. As brentuximab vedotin does not bind to CD30 from rats, toxicity findings in the rat studies should be considered with caution. The toxicity of the antibody component (cAC10) and the cytotoxic component (MMAE) of brentuximab vedotin was also assessed in both animal species. All pivotal studies were GLP compliant and were adequately conducted with appropriate group sizes and suitable monitoring and analyses performed. The clinical dosage regimen (once per 3 weeks) was used in the longer term monkey studies (greater than or equal to 11 week studies), while once weekly

[6] Using a mg/kg to mg/m^2 conversion factor of 6, 12 and 33 for rats, monkeys and humans, respectively.
[7] The molecular weight for MMAE is 718 and the molecular weight for brentuximab vedotin is 153, 352. A dose of 100 µg/kg MMAE to rats corresponds to 139 nmol/kg or 834 nmol/m^2, which is ≈209 nmol/m^2 brentuximab vedotin. A clinical dose of 1.8 mg/kg brentuximab vedotin corresponds to 12 nmol/kg or 396 nmol/m^2.

dosing was used in the pivotal rat study. The duration of the pivotal monkey study is acceptable according to the relevant guidelines (ICH S9 and ICH S6(R1)). The duration of the rat studies, however, is rather short. While normally at least one 3 month repeat-dose toxicity study in rats would have been expected, it is not considered necessary for this drug (and the proposed indication) due to the lack of pharmacological activity of the cAC10-component of brentuximab vedotin in rats. Doses used in the studies were appropriate, limited by severe toxicity. Unfortunately, accompanying adequate toxicokinetic data were only available in a handful of studies. Relative exposures to brentuximab vedotin and MMAE in the submitted studies were similar to or below the clinical exposure.

Relative exposure

The relative exposure of monkeys to brentuximab vedotin was determined by direct comparison of the $AUC_{0\text{-}21\ days}$ for the parent drug in both species. The relative exposure of cAC10 in monkeys was determined by initially converting the AUC data from mg.h/mL to µg.day/mL, adjusting for once/week compared with once per 3 weeks clinical dosing by multiplying by 3 (to obtain an area under the curve during 21 days ($AUC_{0\text{-}21\ days}$) for cAC10) and then comparing the $AUC_{0\text{-}21\ days}$ for cAC10 in monkeys with the $AUC_{0\text{-}21\ days}$ for total drug antibody in patients. Exposures to MMAE were based on the free fraction (27% free in rats, 82% free in monkeys and 25% free in humans).

Table 1. Relative exposure in repeat-dose toxicity studies

Species	Study duration (dosing regimen)	Test item	Dose (mg/kg)	$AUC_{0-21\ d}$ (µg·day /mL)	$AUC_{0-21\ d}$ (ng·day /mL)	Exposure ratio	
				Brent. vedotin	MMAE[#]	Brent. vedotin	MMAE
Rat (SD)	7646-118 *4 weeks* (once/week)	MMAE	0.0097	–	2.86	–	0.28
			0.097	–	32.8	–	3
			0.194	–	48.7	–	5
Monkey (Cynomolgus)	1151-167 *6 weeks* (once/week)	cAC10	10	3849[a]	–	22[b]	–
			50	27624[a]	–	154[b]	–
			100	47250[a]	–	264[b]	–
	8216375 *6 months* (once/3 weeks)	Brentuximab vedotin	1	6.29	5.67	0.07	0.5
			3	145	8.2	1.7	0.8
Human	–	Brentuximab vedotin	1	84.0	10.4	–	

[#] $AUC_{0\text{-}21d}$ values of unbound MMAE; [a] $AUC_{0\text{-}\infty}$ data for cAC10 based on first dose.

Major toxicities

The major target organs for brentuximab vedotin were similar to those for MMAE and were similar to currently-registered tubulin-acting cytotoxic compounds and included the liver, bone marrow, male reproductive organs and gastrointestinal tract. The only notable finding with the antibody component of brentuximab vedotin, cAC10, was a slight reduction (by less than or equal to 20%) in T-lymphocytes. This might be attributed to the anti-CD30 activity on CD30-expressing T-lymphocytes. Given the high exposure margins for the antibody component and the minimal reduction in T-lymphocytes, this finding is not considered to be clinically-meaningful. Overall, the toxicity findings with brentuximab vedotin can be attributed to the MMAE component of the compound, and given the low exposure margins, the following findings should be considered as clinically-relevant.

Myelotoxicity was characterised by bone marrow hypocellularity (affecting most haematopoietic precursors), with accompanying reductions in red blood cell components, lymphocytes, monocytes, basophils, eosinophils and neutrophils. Sepsis as a result of severe neutropaenia contributed to the death of 3 monkeys that received 6 mg/kg/3 weeks IV brentuximab vedotin. Due to the severe neutropaenia in this study with 6 mg/kg brentuximab vedotin and 0.058 mg/kg MMAE (molar equivalent to 3 mg/kg brentuximab vedotin), it was necessary to administer antibiotics to reduce the risk of opportunistic infections. Changes were also seen in the lymphoid organs, including atrophy of the white pulp of the spleen, haemosiderin in the red pulp of the spleen and mild hypocellularity and/or apoptosis of the cortical lymphocytes in the thymus. The bone marrow and lymphoid changes (and accompanying haematological effects) were shown to be reversible with the cessation of treatment. No histopathological changes were seen in the pivotal monkey study at less than or equal to 3 mg/kg/3 weeks IV brentuximab vedotin (relative exposure: 1.7 for brentuximab vedotin, 0.8 for MMAE corrected for plasma protein binding). The data in monkeys indicate that at molar equivalent doses, greater myelotoxicity was seen with MMAE than brentuximab vedotin.

The male reproductive organs of rats were a target for toxicity with brentuximab vedotin and MMAE. Moderate to severe seminiferous tubular degeneration and necrosis was seen in the testes of male rats treated with 10 mg/kg/week IV brentuximab vedotin. Sertoli cell vacuolation was seen at 5 mg/kg brentuximab vedotin. Reduced spermatocytes in the testes with epididymal aspermia were seen in rats treated with greater than or equal to 5 mg/kg IV brentuximab vedotin or 194 µg/kg IV MMAE (relative exposure for MMAE: 5). No changes in male reproductive organs were observed at 0.5 mg/kg. A mechanistic study indicated the testicular findings were only partially reversible with multifocal, minimal to severe seminiferous tubular degeneration and necrosis still evident in some animals 16 weeks after the last dose. Although there were no testicular changes in the monkey studies, the Nonclinical Overview states that the sexual immaturity of the monkeys in these studies means that no firm conclusions regarding the potential for testicular toxicity in this species can be drawn from the submitted data. However, as most of the toxicity findings can be attributed to MMAE, a microtubule acting agent, the testes, a known target organ for these types of drugs, should be considered as a target organ for toxicity with brentuximab vedotin.

Some signs of gastrointestinal disturbance were seen across the single-dose and repeat-dose toxicity studies. Soft faeces were seen in rats that received a single dose of MMAE (50 µg/kg IV) or brentuximab vedotin (1.5 mg/kg IV), and monkeys that received repeated doses of greater than or equal to 1 mg/kg/3 weeks IV brentuximab vedotin (less than clinical exposure to brentuximab vedotin and MMAE). Emesis and inappetance were seen in monkeys that received a single dose of 166 µg/kg IV MMAE and repeated doses of greater than or equal to 1 mg/kg/3 weeks IV brentuximab vedotin. Histopathological changes were only seen in the single-dose toxicity studies with single cell necrosis seen in the intestines of rats that received 7.5 mg/kg IV brentuximab vedotin or 250 µg/kg IV MMAE (relative exposure: greater than 5). These findings are typical for those seen with other tubulin-acting compounds. Nausea and vomiting may be seen during clinical use.

Hepatobiliary toxicity was evident in rats, with elevated gamma-glutamyl transpeptidase (GGT) (up to 8 times), aspartate aminotransferase (AST) (up to 17 times) and/or alanine transaminase (ALT) (up to 5 times) levels in rats treated with greater than or equal to 0.5 mg/kg/week IV brentuximab vedotin or greater than or equal to 194 µg/kg IV MMAE. Liver damage was seen during post-mortem analyses of rats treated with greater than or equal to 97 µg/kg/week IV MMAE and greater than or equal to 5 mg/kg/week IV brentuximab vedotin; histological lesions included bile duct hyperplasia, increased mitotic indices and single cell necrosis. Signs of liver toxicity were less prominent in monkeys and consisted only of elevated liver enzymes – AST (up to 3 times) in monkeys treated with a

single dose of 116 µg/kg IV MMAE and repeated doses of 6 mg/kg/3 weeks IV brentuximab vedotin. Elevated ALT levels were only seen in the single-dose monkey toxicity studies at 1 mg/kg IV brentuximab vedotin. There was no evidence of elevated ALT levels with repeated doses of less than or equal to 6 mg/kg/3 weeks IV brentuximab vedotin and no evidence of liver damage during post-mortem analyses. The findings in rats, at least, suggest that liver damage may be seen during clinical use; however, this should be easily monitored (LFTs) and was shown to be mostly reversible.

Peripheral neuropathy was reported as a common adverse effect in clinical trials with brentuximab vedotin. Hindlimb paralysis (but in the absence of histopathological changes) in rats treated with greater than or equal to 200 µg/kg IV MMAE was the only evidence of neurotoxicity in the submitted studies. Therefore, this adverse effect was not well predicted from the animal data. However, peripheral neuropathy is a common adverse effect of tubulin-acting drugs[8].

Genotoxicity

The potential genotoxicity of brentuximab vedotin was not assessed, which is generally acceptable for a biotechnology product (ICHS6(R1)). However, the potential genotoxicity of the small molecule components of brentuximab vedotin, MMAE and the linker, was considered in submitted studies and literature references. The potential genotoxicity of MMAE was assessed in the standard battery of tests (bacterial mutagenicity study, mouse lymphoma test and rat micronucleus study) conducted in accordance with ICH guidelines. All assays were appropriately validated and conducted under GLP conditions. Negative results were returned in the bacterial mutation assay and the forward mutation assay in mouse lymphoma cells. In the rat micronucleus assay, MMAE induced bone marrow toxicity and an increase in micronucleated polychromatic erythrocytes was observed. The micronuclei induced by MMAE were generally centromere positive (60 to 76%), suggesting an aneugenic mode of action. This is consistent with other tubulin-acting agents.

The linker component of brentuximab vedotin contains maleimide, caproic acid, valine, citrulline and p-aminobenzylcarbamate. Caproic acid, valine and citrulline are endogenous compounds and may be considered non-genotoxic. Maleimide, however, was positive in the bacterial mutation assay and mouse lymphoma assay (National Library of Medicine chemical carcinogenesis research information system (CCRIS) Database). No data were provided regarding the potential genotoxicity of p-aminobenzyl carbamate. This is not considered a deficiency given the intended patient population and data with maleimide and MMAE provide sufficient evidence that brentuximab vedotin should be considered genotoxic.

Carcinogenicity

No carcinogenicity studies have been conducted with brentuximab vedotin, which is considered acceptable given the proposed indication. Based on positive findings in genotoxicity tests with some of the small molecule components of brentuximab vedotin, the latter compound should be considered a probable human carcinogen.

Reproductive toxicity

Reproductive toxicity studies were restricted to effects on embryofoetal development in rats. The absence of fertility and pre/postnatal studies is acceptable considering the

[8] Wozniak, K.M., Nomoto, K., Lapidus, R.G. *et al.* (2011) Comparison of Neuropathy-Inducing Effects of Eribulin Mesylate, Paclitaxel, and Ixabepilone in Mice. *Cancer Res.* **71:** 3952–3962.

intended indication and patient group (ICH S9: Nonclinical Evaluation for Anticancer Pharmaceuticals). Nevertheless, findings in male rats in the repeat-dose toxicity studies (see the Repeat-dose toxicity section), combined with its aneugenic activity, both attributable to MMAE, indicate brentuximab vedotin may have adverse effects on fertility (both males and females). Given the testicular lesions had not reversed by 16 weeks after the last dose, though a trend to reversion was evident, combined with the long half-life of brentuximab vedotin ($t_{1/2}$ 4.4 days), treated men should avoid fathering a child during treatment and at least for several months after the final dose.

Brentuximab vedotin crossed the placenta in rats and could be detected in the amniotic fluid and foetal serum, albeit at lower levels than those in maternal serum. MMAE levels, however, were consistently higher in foetal serum and amniotic fluid than in maternal serum, regardless of whether the test item was brentuximab vedotin or MMAE. Transfer of brentuximab vedotin was likely via the Fc receptor. Generally, foetal serum:maternal serum ratios of MMAE were higher with brentuximab vedotin than with MMAE alone, which may be due to direct placental transfer of MMAE, as well as formation of MMAE following placental transfer of brentuximab vedotin. Embryofetal development toxicity was assessed in a single species, rats. Sufficient animal numbers were used in the pivotal study and dosing was once per week during the period of organogenesis. Exposures, however, were similar to or below the anticipated clinical exposure to MMAE and brentuximab vedotin but were the maximum tolerated. Generally, it would be expected that embryo foetal toxicity would be assessed in two species; however, there is sufficient evidence in rats to indicate the potential for embryo foetal toxicity and embryo foetal lethality with the clinical use of brentuximab vedotin.

Table 2. Relative exposure in embryo foetal development study

Species	Test item	Dose (mg/kg IV)	AUC_{0-last}		Exposure ratio# based on	
			Bren. ved. (µg·day/mL)	MMAE (ng·day/mL)	Bren. ved.	MMAE
Rat (SD) Study 8204397 GD13 data	Brentuximab vedotin	0.3	6.01	NR	0.08	–
		1	22.7	0.149	0.3	0.004
		3	80.2	0.469	1	0.01
		10[a]	405	2.14	5	0.06
	MMAE	0.2	–	26	–	0.7
Human (patients)	Brentuximab vedotin	1.8	79.4[b]	37[b]	–	–

= animal:human plasma AUC; [a]no viable foetuses; [b]$AUC_{0-\infty}$; – = not relevant; NR = not reportable

Marked post-implantation loss (mainly due to early resorptions and possibly attributable to the aneugenic activity of MMAE) was seen at greater than or equal to 3 mg/kg IV brentuximab vedotin (approximately 0.058 mg/kg MMAE) (almost 100%) and 0.2 mg/kg IV MMAE (27%). The greater incidence of embryo foetal lethality with brentuximab vedotin compared with MMAE is likely due to the longer half-life of MMAE when administered as part of brentuximab vedotin (leading to a longer duration of embryo foetal exposure) and higher foetal exposure to MMAE compared with when MMAE is administered on its own. No embryo foetal deaths were seen at less than or equal to 1 mg/kg IV brentuximab vedotin, resulting in subclinical levels of both brentuximab vedotin and MMAE. Decreased foetal weights were observed with brentuximab vedotin at 3 mg/kg. Foetal malformations were observed at all doses and included: umbilical hernia and malrotated hind limbs (one foetus at 3 mg/kg brentuximab vedotin); protruding tongue, malrotated hind limbs, gastroschisis and agnathia (3 foetuses (3 litters) in the MMAE group); situs inversus (one foetus each in the 0.3 mg/kg brentuximab vedotin and 0.2 mg/kg MMAE groups (none in historical control data)); and malformed mandible, misaligned, fused and/or absent caudal vertebrae, split vertebrae, and shortened long bone (2 foetuses (2 litters) in the MMAE group). Given these findings occurred at exposures at or below the clinical exposure and can be attributed to MMAE

pharmacological action (the anti-CD30 effects were not assessed in this animal model), a risk to a developing foetus should be considered during clinical use. Furthermore, given the long half-half of brentuximab vedotin, a sufficient washout period would be recommended before a female patient considers becoming pregnant.

Pregnancy classification

The sponsor has proposed Pregnancy Category D.[9] Given the embryo lethality and foetal malformations seen following brentuximab vedotin dosing to rats, the proposed category is considered appropriate. This category is consistent with other anti-tubulin medicines.

Local tolerance

Specialised local tolerance studies were not conducted but local reactions, including signs of anaphylaxis, were assessed in repeat-dose toxicity studies with the clinical formulation and concentration. No drug-related findings were noted.

Immunogenicity

Anti-drug antibodies (ADAs) were not detected in rats treated with brentuximab vedotin in the pivotal rat toxicity study. ADA induction was not assessed in the other rat studies. ADAs were induced in brentuximab vedotin-treated monkeys and could be consistently detected in animals from all treatment groups. In the pivotal 6 month monkey study, 39 out of 40 animals had detectable ADAs. ADA production led to lower exposures to brentuximab vedotin and higher exposures (up to 48 times) to MMAE in affected animals. While animal data in regard to immunogenicity are not always predictive of the clinical situation, the data in monkeys suggest there is a risk for greater toxicity (as a result of increased MMAE exposures) in subjects in which ADAs had been induced. The proposed Product Information document states that approximately 35% of patients with relapsed or refractory HL or sALCL developed ADAs in two Phase II studies. It states that the presence of antibodies to brentuximab vedotin did not correlate with a clinically-meaningful reduction in serum brentuximab vedotin levels and did not result in a decrease in the efficacy of brentuximab vedotin. This requires confirmation by the Clinical Evaluator.

Immunotoxicity

As stated in the Repeat-dose toxicity section, myelotoxicity was a dose-limiting toxicity, particularly in monkeys. Brentuximab vedotin treatment to both rats and monkeys, resulted in severe reductions in the level of white blood cells (neutrophils, monocytes, eosinophils and lymphocytes), sometimes to undetectable levels in the case of neutrophils and eosinophils. In the 11 week toxicity study in Cynomolgus monkeys (Study SNBL-163-16), antibiotics were given to animals treated with 6 mg/kg/3 weeks IV weeks brentuximab vedotin (estimated exposure area under the curve (AUC) ratio for MMAE, 2) to reduce the risk of opportunistic infections, while in a single-dose study with MMAE (116 μg/kg IV), the death of one animal was suggested to be due to pneumonia, likely as a result of severe immunosuppression. The severe leukopaenia (in particular neutropaenia and eosinopaenia) seen in monkeys with brentuximab vedotin, suggest a risk for opportunistic infections during clinical use.

[9] Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

Paediatric use

Brentuximab vedotin is not proposed for paediatric use and no specific studies in juvenile animals were submitted. Findings in animal studies that would be particularly relevant for a paediatric indication include the bone marrow toxicity and effects on the thymus and testes. In the Nonclinical Safety Specification of the Risk Management Plan, the sponsor states that an immunotoxicity study will be conducted in Cynomolgus monkeys aged 2 to 3 years. The report for this study should be submitted to the TGA as soon as it is available.

Nonclinical summary and conclusions

- The primary pharmacology studies support the proposed clinical use of brentuximab vedotin in patients with CD30-positive HL or sALCL.
- Inhibitors/inducers of CYP3A4 or P-glycoprotein are likely to alter the plasma kinetics of MMAE, thereby affecting the safety and efficacy profile of the drug.
- The toxicity findings with brentuximab vedotin can be attributed to MMAE and are typical for those seen with tubulin-acting agents. Notable findings of clinical relevance in the toxicity studies include:
  - Reversible myelotoxicity with secondary haematological effects (both anaemia and leukopaenia), indicating a risk for opportunistic infections;
  - Gastrointestinal disturbances (vomiting and nausea);
  - Reduced male fertility and effects on the testes, which was not completely reversible after a 16-week treatment-free period in rats;
  - Reversible hepatotoxicity, which should be easily monitored;
  - Embryofoetal lethality and foetotoxicity
- The clinical relevance of the effects of anti-drug antibody production in monkeys is unknown.
- Given the effects on the testes, the aneugenic properties of MMAE and the adverse embryo foetal effects, together with the long half-life of brentuximab vedotin, a washout period of more than 2.5 months would be recommended before patients consider becoming pregnant.
- There are no objections on nonclinical grounds to the registration of brentuximab vedotin for the proposed indications.

Amendments to the draft PI were recommended by the nonclinical evaluator but these are beyond the scope of this AusPAR.

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.

Clinical rationale

Hodgkin's lymphoma is a relatively uncommon haematological disease that usually responds extremely well to frontline therapy for patients who have received little in the way of prior treatment. For the sub-set of patients with relapsed disease sensitive to salvage chemotherapy current ablative regimens followed by autologous stem cell transplant (ASCT) may represent a curative approach. However for those patients with

primary refractory disease and those who failed to experience a complete response for second line treatments and those who are otherwise not candidates for ASCT and those who relapse following ASCT no therapies have been shown to be effective. Accordingly Adcetris has been evaluated in this patient population of Hodgkin's disease.

Anaplastic large cell lymphoma (ALCL) is a very rare aggressive lymphoma that is potentially curable with frontline multi agent chemotherapy. However approximately half of these patients develop recurrent disease for which current multi agent and/or single agent salvage therapy generally is associated with limited benefit. Accordingly Adcetris has been evaluated in this patient population.

Contents of the clinical dossier

The clinical dossier involved a total of six studies presented;

- Two Phase I dose escalation studies in patients with relapsed or refractory CD30+ malignancies, (that is, Studies 0001 and 0002 both of which also contain PK data,)
- A pivotal single arm Phase II study in relapsed or refractory HL post ASCT, Study 0003, and
- A pivotal single arm Phase II study in relapsed or refractory sALCL (0004).
- Two Phase I clinical pharmacology studies including an intensive corrected QT interval, QT interval study, Study 007 and
- A clinical pharmacology study with a drug to drug interaction/excretion arm Study 008A.
- Also included was a population pharmacokinetic analysis derived from the six studies.

Paediatric data

This submission did not include paediatric data.

Good clinical practice

All aspects of good clinical practice were observed in the studies included in this application.

Pharmacokinetics

Studies providing pharmacokinetic (PK) data

Four clinical studies provide the primary clinical pharmacology data. Studies 0001 and 0002 which were Phase I studies evaluating PK and anti-tumour response and safety to Adcetris:

- Study 007 which was designed to assess the effects of Adcetris on cardiac ventricular repolarisation, and
- Study 008A was designed to determine the drug to drug interaction between Adcetris and substrates of Cytochrome P450s (CYP) or modulators of CYP function and the routes of excretion of MMAE.

Additional sparse PK data from the two pivotal Phase II studies namely Studies 0003 and 0004 were also included in the population PK model.

The pharmacokinetic programme characterised the PK profile of three analytes, that is brentuximab vedotin antibody drug conjugate (ADC); mono-methyl auristatin (released small molecule) or MMAE; total antibody or ADC plus unconjugated cAC10 antibody (TAb). All studies used sensitive validated assays to measure the concentration of analytes. These assays included enzyme linked immunosorbent assays, liquid chromatography coupled to tandem mass spectrometry assays and other assays as required.

Evaluator's conclusions on pharmacokinetics

Whilst further discussion can be found in the Clinical Evaluation Report Extract (CER) at Attachment 2, PK data have shown a quite comprehensive determination of a PK for Adcetris. No untoward relationships were determined from these analyses.

Dosage selection for the pivotal studies

In the Phase I Study 0001 a dose of 1.8 mg/kg administered every three weeks was determined to be the maximum tolerated dose and the proportion of dose limiting toxicities were significantly less at 1.8 mg/kg compared to 2.7 mg/kg. To be discussed below the objective response rate of this dose level for both HL and ALCL are indicative of significant potential clinical efficacy.

It was noted that from Study 0002 the prolonged weekly dosing of at least four months duration resulted in an onset of peripheral neuropathy in approximately three quarters of patients. The objective response rate for patients with HL and ALCL was similar to the three weekly schedule and the incidence of adverse effects appeared to be significantly less with the dose schedule of 1.8 mg/kg every three weeks and was chosen for the Phase II studies.

Efficacy

Studies providing efficacy data

Phase I studies

Two Phase I studies presented in this evaluation namely 0001 and 0002 provided data with relevance to efficacy.

Hodgkin's lymphoma studies

The pivotal Study 0003 was a Phase II single arm open label multicentre study utilising brentuximab vedotin in a dose of 1.8 mg/kg intravenously every three weeks as a single agent in patients with relapsed or refractory HL. The primary objective was to assess efficacy based on the objective response rate. Secondary objectives were to assess duration of tumour control including duration of response and progression free survival, overall survival, safety and tolerability. Patients could remain on treatment for up to 16 cycles or approximately one year or until disease progression which ever occurred earlier. A minimum treatment period of eight cycles was recommended for patients with objective response or stable disease. Patient enrolment was approximately 100 patients.

Systemic anaplastic large cell lymphoma (sALCL) studies

Study 0004 was a pivotal Phase II single arm open label multicentre study of brentuximab vedotin at a dose of 1.8 mg/kg IV every three weeks as a single agent in patients with relapsed or refractory sALCL. The primary objective was to assess the efficacy of brentuximab vedotin as measured by overall response rate. Secondary objectives were to assess complete response rate, duration of response and progression free survival, overall

survival. Additional efficacy objectives included the assessment of disease related symptoms and the correlation of potential biomarkers of clinical outcome. Patients could remain on treatment for up to 16 cycles or approximately one year or until disease progression which ever occurred earlier. A minimum treatment period of eight cycles was recommended for patients achieving an objective response or stable disease. Planned enrolment was approximately 55 patients. Eligible patients had previously received multi-agent frontline therapy with curative intent and were ambulatory with an ECOG status 0/1.

Further discussion of Studies 0001, 0002, 0003 and 0004 may be found in the CER.

Evaluator's conclusions on efficacy

Phase I studies

This data clearly demonstrated a significant level of efficacy for patients with very advanced stage Hodgkin's disease receiving Adcetris as monotherapy. With an overall response rate of 75% and a complete response rate of 33% with a median duration of progression free survival of 5.6 months and a 24 month 23% PFS this is very impressive. Similarly estimates of median overall survival of 27 months and evidence of efficacy across all analyses there is strong evidence that Adcetris represents a new agent of clinical utility in the treatment of patients with advanced stage Hodgkin's disease.

Hodgkin's lymphoma studies

This data have clearly demonstrated a significant level of efficacy for patients with very advanced stage Hodgkin's disease receiving Adcetris as monotherapy. With an overall response rate of 75% and a complete response rate of 33% with a median duration of progression free survival of 5.6 months and a 24 month 23% PFS this is very impressive. Similarly estimates of median overall survival of 27 months and evidence of efficacy across all analyses there is strong evidence that Adcetris represents a new agent of clinical utility in the treatment of patients with advanced stage Hodgkin's disease.

Systemic anaplastic large cell lymphoma (sALCL) studies

An overall response rate for Adcetris in patients with heavily previously treated systemic ALCL was 86% with a CR rate of 59%. This is very impressive and backed up by median progression free survival of 14.3 months and a median duration of overall survival was not reached. This therefore represents a clear indication of significant clinical benefit for Adcetris in this setting for patients with systemic ALCL.

Safety

Studies providing safety data

The clinical safety programme for evaluation in this submission includes the six completed clinical studies in patients with CD30+ haematological malignancies which include Studies 0001, 0002, 0003, 0004, 007 and 008A.

Safety issues with the potential for major regulatory impact

Approximately half of the patients in the Phase II study experienced treatment emergent peripheral neuropathy which was primarily mild to moderate and the most frequently occurring events were peripheral sensory neuropathy in 45%, peripheral motor neuropathy in 9% and paraesthesia in 6%. Grade III peripheral neuropathy events occurred in 21 patients or 13%. No Grade IV events were reported. Peripheral motor neuropathy events were observed in 9% and Grade III motor events were reported in 2%

of patients. The median time to onset for any peripheral neuropathy event was 12.4 weeks and those which were classified as at least Grade III tend to occur in later cycles with the majority of events having first onset between cycles 9 and 16. A total of 18% of patients required dose modification for peripheral neuropathy with dose delays occurring in 24 patients or 15% and dose reductions in 14 patients or 9%. Treatment discontinuations for peripheral neuropathy occurred 19 patients or 12% in the Phase II study.

The neuropathy was generally reversible with median time from onset to resolution or improvement of peripheral neuropathy symptoms being approximately 16 weeks. For those patients whose neuropathy did not completely resolve were generally left with a Grade I/II level of neuropathy.

In relation to neutropenia, this was a relatively common treatment emergent adverse event with an incidence of 21% in the Phase II studies. Grade III and IV neutropenia occurred in 13 and 7% of patients respectively. Neutropenia appeared to be well managed with protocol specified recommendations for hematologic toxicity, that is dose delay, growth factor support. The median duration of Grade III or IV neutropenia was limited to one week and only three patients had Grade IV neutropenia that lasted more than this. Less than half of the patients with neutropenia had temporally associated infections and the majority of temporally associated infections were Grade I or II. The relative dose intensity in the Phase II studies was > 90% indicating that the dose withholding for neutropenia had a minimal impact on overall Adcetris dosing.

Infections were observed in 61% of patients in the Phase II study. The majority of these infections were Grade I or II and occurred with an incidence comparable to that reported in similar populations. No patient discontinued treatment due to infection and infection led to dose delay in only 11% of patients. The most frequent grade infections were Grade I or II URTI which was more frequent in HL patients. Grade III/IV infections occurred in < 10% of patients and there were no Grade V infections. No specific pattern of serious infections could be discerned and the majority are not considered by the investigator to be related to Adcetris and none led to treatment discontinuation.

In relation to infusion related reactions, adverse events considered by the investigator to represent possible infusional reactions occurred in 11% of patients in the Phase II studies. A similar rate was observed in the Phase I studies. Nearly all events were mild to moderate in severity and most occurred in the first two treatment cycles. The most common of these included chills, nausea, dyspnoea and pruritis and cough. Two cases of infusional related anaphylaxis occurred in the Phase I studies.

Infusion interruption for these reactions resulted in successful completion of the dose in most cases and continued treatment with Adcetris with or without subsequent prophylaxis was generally possible. It is to be noted that if anaphylaxis occurs then treatment requires discontinuation.

It is noted that one patient experienced a tumour lysis syndrome on the first day of treatment with Adcetris requiring relevant acute phase management. This patient however was subsequently able to resume Adcetris.

One patient experienced a Stevens-Johnson syndrome during the second cycle of treatment. This condition resolved with appropriate therapy and the patient permanently discontinued Adcetris.

A total of 6% of patients developed hyperglycaemia during treatment with Adcetris which was Grade III or IV in 4% of patients. This tended to occur early in treatment and the elevated glucose levels were generally well controlled with appropriate anti-hyperglycaemic therapy.

It is noted that two reports of progressive multi focal leukocoencephalopathy has been reported. Both cases occurred in patients with multiple risk factors for developing this

condition and it not clear whether this condition may have relationship to Adcetris therapy.

In relation to laboratory evaluation, central laboratory data was collected only pre dose for each treatment cycle in the Phase II trial. Few patients overall had post baseline worsening to Grade III or higher in clinical laboratory values. The most common of these was associated with low neutrophils, lymphocytes, platelets, high glucose and leucocytes. Only one patient in the Phase II studies had a Grade III elevated ALT and AST. No significant changes in vital signs were noted during the course of the various studies.

In relation to immunogenicity, blood samples for assessment of this were to be collected at baseline within two hours before administration of each dose of Adcetris and at the end of treatment. Within each study approximately one third of patients, that is 33 to 39% had at least one post baseline ATA+ result and 4 to 11% of patients tested positive for ATA at baseline. The incidence of ATA tended to be highest at cycle 2 and decreased in subsequent cycles. In the Phase II studies trends towards a higher incidence of adverse events in persistently positive patients relative to transiently positive or negative patients were not apparent except for a slightly higher incidence of infusion related reactions in persistently positive patients at 27% relative to transiently positive at 12% and negative in 7% of patients. These events however were Grade I and II without any cases of anaphylaxis.

Generally patients categorised as persistently positive on average tended to stay on treatment slightly longer relative to other patients. ATA titres were generally low, however two patients with high titre persistently positive ATA discontinued treatment because of infusion related reactions or adverse events or consistent with infusion related reactions. It is noted that three additional patients in the Phase II studies exhibited ATA titres > 125 however they all completed the maximum 16 cycles of treatment.

It is noted that in the Phase I Study 007 high persistent titres of ATA at 625 were observed in a patient who experienced a serious adverse event of anaphylactic reaction and Grade III hypoxia upon initiation of the cycle 2 dose.

Post marketing data

No relevant post marketing experience is yet available for Adcetris for the proposed indications.

Evaluator's conclusions on safety

While TEAEs occurred in at least 20% of patients in the Phase II studies most often being peripheral sensory neuropathy in 45%, fatigue in 43%, nausea in 41%, diarrhoea in 34%, pyrexia in 31%, upper respiratory tract infection in 31%, neutropenia in 21% and vomiting in 20%, these events were most often mild to moderate in severity and reversible. Approximately half the patients had treatment emergent peripheral neuropathy that was predominantly sensory with an onset and severity pattern consistent with a cumulative antitubulin mediated neuropathy. Dose delays and subsequent reduction to 1.2 mg/kg were generally effective in managing peripheral neuropathy. While Grade III and IV neutropenia occurred in 13% and 7% of patients respectively this is generally of short duration and well managed by brief dose delays with some cases requiring growth factor support. Overall this adverse effect profile would indicate that with appropriate monitoring and management patients could be expected to tolerate Adcetris in line with other currently marketed anti-neoplastic agents.

First round benefit-risk assessment

First round assessment of benefits

Hodgkin's lymphoma

The pivotal Study 0003 enrolled 102 patients with relapsed or refractory Hodgkin's lymphoma post ASCT. Each patient received a median of 3.5 prior treatments with a range of 1 to 13 excluding transplant. Also 72 patients had received one line of therapy post ASCT and 49% multiple lines of treatment post ASCT ranging from 2 to 11. Of these 102 patients, nine had not achieved a complete response with any prior line of therapy. The ITT analysis of response per the independent review faculty showed 33% of patients achieved a complete remission and 41% of patients achieved a partial response for an overall response rate of 75%. The median duration of response was 6.7 months and for those patients achieving a CR the median duration of response had not been reached. The estimated median progression free survival was 5.6 months and the estimated median overall survival was 27 months. Various analyses also confirmed this level of benefit associated with Adcetris in patients with heavily pre treated Hodgkin's lymphoma. In particular it is noteworthy that 5 out of 9 patients who had achieved no response to any prior therapy achieved a best response of complete remission following Adcetris. It is also noteworthy that distinct from currently available therapies, benefits with Adcetris as assessed by progression free survival do not seem to be particularly affected by prior therapy. This may therefore suggest a potential to overcome cross resistance to previous chemotherapy for Adcetris.

Systemic anaplastic large cell lymphoma

Previously untreated sALCL is generally associated with a high response rate to frontline chemotherapy but some 50% of patients subsequently relapse and prove refractory to additional treatments. The pivotal Study 0004 enrolled 58 patients with sALCL whose disease was refractory or had relapsed. Patients who had received a median of two prior treatments with a range of 1 to 6 excluding transplant. Of these 58 patients, 36 or 62% had not achieved a complete response or had relapse within three months of frontline therapy. ITT analysis of response per IRF to Adcetris in this pivotal study revealed a 59% complete response rate and a 28% partial response rate for an overall response rate of 86%. The median duration of response was 13.2 months with a range of 0.1 – 21.7+ months and for patients with a CR the median duration of response was not reached with a range of 0.7 – 21.7+ months. The estimated median progression free survival was 14.3 months with a range of 0.8 – 23.6+ months. The estimated median overall survival has not been reached with a range of 0.8 – 23.8+ months. The estimated 12 months overall survival rate was 70% and the estimated 24 month overall survival rate was 66%.

It is noteworthy that activity of Adcetris was noted in this study irrespective of ALK status and also meaningful clinical benefit was noted in patients whose disease had progressed rapidly following treatment with an earlier line of treatment.

First round assessment of risks

A total of 160 patients with HL and sALCL from the two pivotal Phase II studies together with a further 140 of the remaining four Phase I/II clinical studies evaluating Adcetris in this submission provided relevant safety data. The most common adverse events reported were peripheral sensory neuropathy, neutropenia and infection. It is considered that the neuropathy is most likely related to MMAE the anti tubulin portion of the ADC. Most of the adverse effects encountered were reversible or could be appropriately managed with relevant prophylaxis or early intervention. It is noted that the tumour lysis syndrome was reported in two patients, Stevens-Johnson syndrome in two patients and progressive

multifocal leukoencephalopathy in two patients recognising the requirement for careful monitoring of patients throughout the duration of treatment with Adcetris.

First round assessment of benefit-risk balance

The very impressive results achieved with the two pivotal studies, 0003 and 0004 for patients with very far advanced HL and sALCL are well beyond those of normal expectations for patients in this category receiving effectively end line chemotherapy. Not only were the responses impressive but the duration of these were considerably longer that might be anticipated. The spectrum of adverse events noted while not inconsiderable at least were generally either manageable or reversible and subsequent appropriate prophylaxis when required could minimise the likelihood of future adverse events such as neutropenia and infusion related reactions. Accordingly there is a strong favour for benefit over risk for the use of Adcetris for patients with far advanced stage Hodgkin's lymphoma and sALCL.

First round recommendation regarding authorisation

This reviewer considers it appropriate to support approval for the proposed indication for Adcetris namely the treatment of adult patients with relapsed or refractory Hodgkin's lymphoma either following or tolerating stem cell transplant or following at least two prior therapies when ASCT or multi-agent chemotherapy was not a treatment option.

Treatment of adult patients with relapsed or refractory systemic anaplastic lymphoma. The proposed dosage of Adcetris at 1.8 mg/kg administered as an intravenous infusion over 30 minutes every three weeks is also supported.

Clinical questions

Follow up data on current ongoing studies would be of interest.

Second round evaluation of clinical data submitted in response to questions

Efficacy

Updated information on progression free survival, overall survival data for the two pivotal Studies 0003 in relapsed or refractory Hodgkin's lymphoma and 0004 in relapsed or refractory systemic anaplastic large cell lymphoma have been provided.

In the Hodgkin's lymphoma study at median observation time of 2.5 years from the first Adcetris dose 59% of patients remained alive at last follow up with a median progression free survival of 4.8 months for patients who are PET+ at cycle four and 29.2 months for those who are PET at cycle four. The median overall survival was 40.5 months for this patient population. The estimated 24 months survival was 65%.

In relation to the pivotal Study 0004 for ALCL with a median observation time from first dose of 22.8 months the median duration of complete remission off treatment was 14.1 months. The median progression free survival for all patients with objective response was 22.8 months. Overall survival data has now been followed to the 19 June 2013 and the median duration of overall survival has not been reached and the estimated overall survival rate at 24 months was 63%.

Ongoing efficacy and safety studies for Hodgkin's lymphoma, ALCL as well as other lymphomas involve single arm as well as randomised trials and also studies involving the utilisation of Adcetris in combination with other chemotherapies. No data is provided at

this time in relation to results from these studies. It is noteworthy that some of these studies involve the use of Adcetris as first line therapy and the outcomes for these trials will be of interest.

Evaluator comment

These data have therefore demonstrated ongoing evidence of efficacy for Adcetris in both Hodgkin's lymphoma and ALCL comparable to that documented in the initial evaluation of the two pivotal studies. The ongoing data from the new studies still remains outstanding and will add evidence in relation to potential roles for Adcetris in other settings including in combination and as first line therapy. The evidence of ongoing long term benefits in relation to survival for both Hodgkin's lymphoma and ALCL are further confirmation of the potential beneficial role for Adcetris in these disease settings.

Safety

Periodic safety update report for the dates from the 19 August 2012 – 18 February 2013 is provided in the Section 31 Response. This updated report indicates that in relation to the proposed indications for both Hodgkin's lymphoma and ALCL that are already under consideration by the TGA that Adcetris has been approved in 29 countries as of the 18 February 2013.

Overall 1457 patients have been enrolled in clinical trials with 1286 patients actually receiving Adcetris.

Post marketing patient exposure to Adcetris has also occurred in 950 patients in the US and 290 patients in the European Union with an estimated cumulative patient exposure for marketing experience of approximately 3690 patients.

Review of the data from these patient populations has demonstrated no changes in the adverse drug reaction profile for Adcetris.

Particular review has been undertaken of high risk toxicities. Three new cases of progressive multifocal leukoencephalopathy (PML) were revealed, which in the context of the overall patient exposure are comparable with that already previously documented in the pivotal studies 002 and 003 and is no higher than the published background rate of PML in patients with lympho-proliferative disorders treated with chemotherapy, namely 0.07% to 0.52%.

A single case of toxic epidermal necrolysis has been reported but this patient was also receiving other medications known to be associated with this toxicity.

A review of new cases of febrile neutropenia received during the reporting period has demonstrated other risk factors for febrile neutropenia were present in all cases and does not suggest a change to the benefit risk/assessment of Adcetris.

Of interest are safety data provided in relation to the utilisation of Adcetris in combination with other chemotherapy. One study 009 which was a Phase I study investigating the combination of Doxorubicin Bleomycin, Vinblastine, Dacarbazine or AVD omitting Bleomycin with both arms combined with Adcetris revealed that an incidence of pulmonary toxicity in the ABVD plus Adcetris arm had increased to 44% relative to historical observations of Bleomycin containing chemotherapy regimens of 10 to 25%. One of these patients had a fatal pulmonary toxicity.

This increased frequency of severity of pulmonary toxicity with this combination has led to a contraindication for concomitant use of Adcetris and Bleomycin. Of note no pulmonary toxicity was observed in patients treated with Adcetris in combination with AVD.

In other studies in relation to combination chemotherapies utilised particularly CHOP combinations or variations thereof, there is no evidence that the addition of Adcetris to these agents is associated with increase in significant safety findings. It is of note however that these studies remain ongoing.

Review of data from other clinical trials and sources involving Adcetris as a single agent in various indications including cutaneous T-cell lymphoma, use of Adcetris in combination with AVD for older patients with untreated Hodgkin's lymphoma, patients with diffuse large cell B-cell lymphoma in the elderly etc. None of these have demonstrated new safety signals of concern. Similarly ongoing literature review for data in relation to the use of Adcetris has not revealed any new safety signals of concern.

Evaluator comments

These updates have indicated evidence for ongoing need to be aware of the potential toxicity of PML in patients receiving Adcetris of this although this does not appear to be clearly greater than that for circumstances in patients with lymphomas receiving other chemotherapy. The requirement for relevant ongoing monitoring and appropriate prophylaxis for patients at risk for febrile neutropenia receiving Adcetris is apparent. The new safety signal of risk of Adcetris in combination with Bleomycin represents a point of likely inclusion in Product Information. Second round benefit-risk assessment.

The data provided represents ongoing evidence of significant benefit for Adcetris in both heavily pre treated patients with Hodgkin's lymphoma and patients with refractory systemic ALCL. Accordingly the data reinforces the clear benefit for this agent in the setting for its proposed indications.

Second round benefit-risk assessment

Overall the data has not provided any evidence of new safety concerns in relation to Adcetris. Certainly as pointed out above the need for appropriate monitoring in relation to potential PML is required. Similarly relevant monitoring and prophylaxis for febrile neutropenia is required. The potential interaction between Adcetris and Bleomycin will likely require ultimate indication in Product Information.

Benefit/risk balance for Adcetris for the proposed indications remains favourable as per the original evaluation.

Second round recommendation regarding authorisation

This evaluator considers that it remains appropriate for approval for Adcetris in relation to the indications:

- *The treatment of adult patients with relapsed or refractory Hodgkin's lymphoma either following autologous stem cell transplant or following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option.*
- *Treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma*

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (European Union Risk Management Plan (EU-RMP) Version 1.0 (dated 10 July 2012, Data lock point (DLP) 19 March 2012) and

Australian-Specific Annex (dated October 2012) which was reviewed by the TGA. This was then superseded by European Union Risk Management Plan (EU-RMP) Version 2.0 (dated 17 April 2013, DLP 18 February 2013) and Australian-Specific Annex Version 2.0 (dated July 2013).

Table 3. Summary of risk management plan

All figures and tables in this section that have been copied from the original dossier are considered by the evaluator to be an accurate representation of the reviewed data, unless qualified as such in the commentary of the report.

Risks	AU Proposed pharmacovigilance activities (routine and additional)	AU Proposed risk minimisation activities (routine and additional)
Important Identified Risks		
Progressive Multifocal Leukoencephalopathy	• Routine Pharmacovigilance	Product Information sections 'Precautions' and 'Adverse Effects' provides data and recommendations
Pulmonary toxicity associated with combination use of bleomycin and brentuximab vedotin	• Routine Pharmacovigilance • Termination of administration of the combination within and without the clinical development programme	Product Information section 'Contraindications' provides recommendations
Peripheral Neuropathy (Sensory and Motor)	• Routine Pharmacovigilance • Ongoing SGN35-0003 study • Ongoing SGN35-0004 study • Ongoing SGN35-005 study • Planned SGN35-014 study • Cutaneous T cell lymphoma study (C25001) • C25003 • Post-authorisation safety study (MA25101) • Planned Post-authorisation study in r/r HL patients ineligible for ASCT	Product Information section 'Dosage & Administration', 'Precautions' and 'Adverse Effects' provides data and recommendations
Neutropenia	• Routine Pharmacovigilance • Post-authorisation safety study (MA25101)	Product Information section 'Dosage & Administration', 'Precautions' and 'Adverse Effects' provides data and recommendations
Thrombocytopenia	• Routine Pharmacovigilance	Product Information sections 'Precautions' and 'Adverse Effects' provides data and

		recommendations
Anaemia	• Routine Pharmacovigilance	Product Information section 'Adverse Effects' provides data
Infection Including Bacteraemia/ Sepsis/Septic Shock	• Routine Pharmacovigilance • Post-authorisation safety study (MA25101)	Product Information sections 'Precautions' and 'Adverse Effects' provides data and recommendations regarding serious infections
Opportunistic Infection	• Routine Pharmacovigilance • Post-authorisation safety study (MA25101)	Product Information sections 'Precautions' and 'Adverse Effects' provides data and recommendations
Infusion-Related Reactions	• Routine Pharmacovigilance • Planned SGN35-014 study • Cutaneous T-cell lymphoma study (C25001) • C25003 • Post-authorisation safety study (MA25101) • Planned Post-authorisation study in r/r HL patients ineligible for ASCT	Product Information sections 'Precautions' and 'Adverse Effects' provides data and recommendations
Hyperglycaemia	• Routine Pharmacovigilance • Post-authorisation safety study (MA25101)	Product Information sections 'Precautions' and 'Adverse Effects' provides data and recommendations
Stevens-Johnson Syndrome	• Routine Pharmacovigilance	Product Information sections 'Precautions' and 'Adverse Effects' provides data and recommendations
Tumour Lysis Syndrome	• Routine Pharmacovigilance	Product Information sections 'Precautions' and 'Adverse Effects' provides data and recommendations
Anti-therapeutic Antibodies	• Routine Pharmacovigilance • Planned SGN35-014 study • Cutaneous T-cell lymphoma study (C25001) • C25003 • Planned Post-authorisation study in r/r HL patients ineligible for ASCT	Product Information sections 'Precautions' and 'Adverse Effects' provides data and recommendations
Important Potential Risks		
Reproductive Toxicity	• Routine Pharmacovigilance	Product Information sections 'Precautions – Effects on Fertility, Use in pregnancy, Use in lactation' provides data and recommendations
Thymus Depletion (Paediatric)	• Routine Pharmacovigilance • Study in cynomolgus monkey (aged 2-3 years) • Study C25002 • Planned Study C25004	Product Information sections 'Precautions – Paediatric Use' provides data and recommendations

Febrile Neutropenia	• Routine Pharmacovigilance • Post-authorisation safety study (MA25101)	Product Information section 'Dosage & Administration', 'Precautions' and 'Adverse Effects' provides data and recommendations
Interaction with Drugs Modifying CYP3A4 Activity	• Routine Pharmacovigilance	Product Information section 'Interactions with Other Medicines' and 'Pharmacology – Pharmacokinetics' provides data and recommendations
Important Missing Information		
Safety in Paediatrics	• Routine Pharmacovigilance • In addition, the agreed PIP includes the following planned studies: ○ Study in cynomolgus monkeys (aged 2-3 years) ○ Study C25002: Phase 1 in paediatric patients (5 to < 18 years) ○ Study C25004: Phase 1 in paediatric patients (5 to < 18 years)	Product Information sections 'Precautions – Paediatric Use' and 'Pharmacology – Pharmacokinetics' provides data and recommendations
Safety in Elderly	• Routine Pharmacovigilance • Post-authorisation safety study (MA25101)	Product Information sections 'Precautions – Use in the Elderly' and 'Pharmacology – Pharmacokinetics' provides data and recommendations
Safety in Patients with Renal, Hepatic, or Cardiac Impairment	• Routine Pharmacovigilance • In addition, Seattle Genetics is conducting a study in patients with hepatic or renal impairment (SGN35-008 [Part B])	Product Information section 'Dosage & Administration', 'Precautions' and 'Pharmacology – Pharmacokinetics' provides data and recommendations regarding renal and hepatic impairment
Long Term Safety	• Routine Pharmacovigilance • Post-authorisation safety Study (MA25101)	As additional data on long term safety with the use of brentuximab vedotin becomes available, additional language will be proposed in the appropriate section(s) of the Product Information

Reconciliation of issues outlined in the RMP report

Table 4 summarises the first round evaluation of the RMP, the sponsor's responses to issues raised by the TGA and the TGA's evaluation of the sponsor's responses.

Table 4. Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	OPR evaluator's comment
Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated section 31 request and/or the Nonclinical and Clinical Evaluation Reports respectively. It is important to ensure that the information provided in response to these include a consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, please provide information that is relevant and necessary to address the issue in the RMP.	'The sponsor acknowledges that further changes to the RMP may be requested and commits to responding to these as they occur.'	
The following should be added as a Potential Risk: Liver toxicity.	'In nonclinical studies, minor liver toxicity was observed in rats who received 5 or 10 mg/kg of brentuximab vedotin intravenously (IV) once weekly for 4 weeks. Toxicity was reversed following the 4-week recovery period and was most pronounced at the high dose levels in rats. Significant alterations in liver function tests were not frequently observed in the clinical studies. In Phase I and II studies, baseline to post baseline grade changes (< 3 to greater than or equal to 3) in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) were observed in 2 or fewer patients for each parameter. Hepatotoxicity and liver function abnormalities have undergone continuous monitoring by the sponsor. In the most recent periodic safety update report (PSUR) (PSUR #1, data lock 18 February 2013), the risk of hepatotoxicity has not been established. Contributing factors to reports of hepatotoxicity and liver function abnormalities referenced in the PSUR included cholestasis from liver lesion compression, graft-versus-host disease, underlying disease, and sepsis. It was determined that while a possible relationship between hepatotoxicity and brentuximab vedotin cannot be excluded, comorbid conditions and concomitant medications are likely to have contributed to the development of hepatotoxicity. Please refer to the PSUR for more details as required. The risk of liver toxicity (hepatotoxicity) remains an open signal and is currently undergoing further evaluation by the sponsor. If liver toxicity is determined to be a potential risk, the EU-RMP for brentuximab vedotin will be updated accordingly. Supporting Documentation: Adcetris PSUR #1 (June 2013)'	In the s 31 response, the sponsor states that 'a possible relationship between hepatotoxicity and brentuximab vedotin cannot be excluded' and '(t)he risk of liver toxicity (hepatotoxicity) remains an open signal and is currently undergoing further evaluation by the sponsor.' The sponsor essentially states that hepatotoxicity is a potential risk. As a result, the recommendation remains unchanged. Liver toxicity should be added as an Important Potential Risk.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	OPR evaluator's comment
The following should be added as Important Missing Information: Non-Caucasian patients;	'The predominant race in the Phase II population was Caucasian (137 out of 160). Although the small number of non-Caucasian patients makes meaningful comparisons among races difficult, the safety profile of brentuximab vedotin in non-Caucasians does not appear markedly different compared with Caucasians. Percentages of Caucasians and non-Caucasians (a) with adverse events (AEs) greater than or equal to Grade 3, (b) who discontinued because of AEs, or (c) who died were similar between the 2 groups. Moreover, no patterns for race as compared to AE incidences within particular Medical Dictionary for Regulatory Activities (MedDRA) System Organ Classes (SOCs) or Preferred Terms were apparent. Study TB-BC010088 is an ongoing Phase I/II study in 20 Japanese patients and will provide additional information on the safety and efficacy of brentuximab vedotin. Study TB-BC010088, a Phase I/II study in 20 Japanese patients diagnosed with relapsed or refractory HL or sALCL, is ongoing. The purpose of the study is to evaluate the efficacy, safety, and pharmacokinetics (PK) of brentuximab vedotin in Japanese subjects with relapsed/refractory CD30+ HL or sALCL. An interim clinical study report (CSR) has been written. The data cut-off date for the interim CSR was 24 September 2012. All 20 subjects had been administered at least 1 dose of brentuximab vedotin and were included in the safety analysis set. The safety profile and the PK profile of brentuximab vedotin were manageable. In the Phase I arm of the study, brentuximab vedotin was evaluated at 1.2 mg/kg IV once every 3 weeks (three weekly). No dose-limiting toxicity was observed in the Phase I arm of the study, and 1.8 mg/kg IV three weekly was determined to be the dose for the Phase II arm of Study TB-BC010088. PK analyses of brentuximab vedotin were characterized at both dose levels of 1.2 mg/kg IV and 1.8 mg/kg IV three weekly. As of the interim data cut-off date, antibody drug conjugate, MMAE, and total antibody levels were considered to be within the acceptable range, based on dosage. As of the interim data cut-off date, no unusual rates or severity of AEs were identified, and no clinically important changes were observed in vital signs, physical examination findings, electrocardiograms, or performance status. There were no notable differences in the safety profiles between the Phase I arm dose of brentuximab vedotin (1.2 mg/kg IV three weekly) and the Phase II arm dose of brentuximab vedotin (1.8 mg/kg IV three weekly). Treatment-emergent AEs of greater than or equal to Grade 3 were observed in 11 patients (55%). Four patients (20%) experienced a serious adverse event (SAE). No AE or SAE led to permanent discontinuation of brentuximab vedotin (TB-BC010088 Interim CSR, Table 10-1), and no patient died during the study as of the interim data cut-off date. Identified AEs of interest were peripheral neuropathy observed in 9 (45%) patients. No peripheral neuropathy event led to a dose reduction. Neutropenia was observed in 11 (55%) patients. AEs under the SOC of Infections and infestations were observed in 10 (50%) patients. Infusion related reaction was not observed in this study. Interim safety data showed that AEs in Japanese patients with refractory or relapsed HL or sALCL in this study who received brentuximab vedotin administered at a dose level of 1.8 mg/kg IV three weekly for up to 16 cycles were manageable. The Study TB-BC010088 interim efficacy data were analysed by an independent review facility (IRF) for Phase II at a dose level	The study conducted by the sponsor only incorporates Japanese subjects. Even if these studies were sufficient to evaluate this population adequately, there are many other non-Caucasians not covered. As a result, Non-Caucasian patients should be added as Important Missing Information and the studies with Japanese subjects presented by the sponsor should be assigned to this Ongoing Safety Concern as additional pharmacovigilance activity.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	OPR evaluator's comment
	of 1.8 mg/kg IV three weekly for up to 16 cycles. The objective response rate (ORR) in 9 out of 9 evaluable patients with relapsed or refractory HL was 67% (95% confidence interval (CI) (29.9, 92.5)). Of the patients with HL (n = 9), 2 patients (22%) had a complete response (CR), 3 patients (33%) had stable disease (SD), and 4 patients (44%) had a partial remission (PR). The ORR in 4 out of 5 evaluable patients with sALCL was 80% (95% CI (28.4, 99.5)). Of patients with sALCL (n = 5), 1 patient was not evaluated, 2 patients (40%) had a CR, and 2 patients (40%) had a PR. In summary, at the time of the interim data cut off, brentuximab vedotin administered at a dose level of 1.8 mg/kg IV three weekly for up to 16 cycles resulted in favourable clinical responses, manageable AEs, and manageable PK profile in Japanese subjects with refractory or relapsed HL or sALCL. For the aforementioned reasons, the sponsor proposes that use of brentuximab vedotin in non-Caucasian patients is not added under Important Missing Information.'	
Use in pregnant patients; and Use in lactating patients.	'Use in pregnancy is included as a precaution in the proposed Australian Product Information for brentuximab vedotin, and this reflects the sponsor's current knowledge and restrictions for use in pregnant and/or lactating women and in women of childbearing potential. In addition, information on the risk of reproductive toxicity that covers the use of brentuximab vedotin in pregnant and lactating women has already been listed as an important potential risk in the EU-RMP. Furthermore, no clinical studies to investigate the effects of brentuximab vedotin in pregnant and/or lactating women are planned, and at this time, no additional measures beyond routine pharmacovigilance are considered necessary. The proposed Product Information text is considered adequate to minimize the use of brentuximab vedotin in pregnant and lactating women. In addition, all relevant safety information pertaining to the use of brentuximab vedotin in pregnancy and lactation will be detailed in future PSURs. Given the aforementioned reasoning, the sponsor feels that there is no justification for including 'use of brentuximab in pregnant and lactating patients' as Important Missing Information. The sponsor therefore proposes that the use of brentuximab vedotin in pregnant and lactating patients should not be included under Important Missing Information.'	This is considered acceptable.
The 'Post-authorisation study in relapsed/refractory HL patients ineligible for ASCT' has neither has a protocol, nor a protocol synopsis available. The sponsor should submit this as soon as possible.	'The cited study, designated C25007, is appended in the Australian Specific Annex to the EU-RMP. Supporting Documentation: Australian Specific Annex to the EU RMP for Adcetris'	This is considered acceptable.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	OPR evaluator's comment
It is noted that the sponsor is planning an open-label clinical pharmacology study of brentuximab vedotin in patients with CD30-positive haematologic malignancies to investigate CYP3A4 drug-drug interactions, excretion, and special populations. The sponsor should assign the following ongoing safety concerns to this study: CYP3A4 interactions, antitherapeutic antibodies.	'The sponsor noted that the study referred to in EU-RMP Question 5 is Study SGN35-008. SGN35-008 Part A is completed; Study SGN35-008 Part B is ongoing. When SGN35-008 Part B is completed, the study is expected to provide information on the behaviour of brentuximab vedotin in patients with hepatic or renal impairment. The results of Study SGN35-008 Part A provided conclusive information about CYP3A4 drug-drug interaction with brentuximab vedotin. The results of Study SGN35-008 part A led to the following conclusions: Co-administration of brentuximab vedotin with ketoconazole, a strong CYP3A4 and P-gp inhibitor, increased the exposure to the antimicrotubule agent MMAE by approximately 73% and did not alter the plasma exposure to brentuximab vedotin. Therefore, co-administration of brentuximab vedotin with strong CYP3A4 and P-gp inhibitors may increase the exposure to MMAE and may increase the risk of neutropenia. Co-administration of brentuximab vedotin with rifampicin, a strong CYP3A4 inducer, did not alter the plasma exposure to brentuximab vedotin; however, it reduced exposure to MMAE by approximately 31%. Co-administration of midazolam, a CYP3A4 substrate, with brentuximab vedotin did not alter the metabolism of midazolam; therefore, brentuximab vedotin is not expected to alter the exposure to medicines that are metabolized by CYP3A4 enzymes. Therefore, there is no additional study needed to address CYP3A4 drug interaction with brentuximab vedotin. The sponsor is monitoring anti-therapeutic antibodies (ATAs) in ongoing and future Studies SGN35-008, SGN35-005, SGN35-014, C25001, C25002, C25006, and C25007. Please refer to the final CSR for Study SGN35-008 Part A for further information. '	This is considered acceptable.
In order to investigate the potential for interactions further, the sponsor should conduct interaction studies to investigate the interaction of brentuximab vedotin with medicines likely to be co-administered (including, but not limited to drugs of the ABVD, CHOP, or BEACOPP escalated regimens, or gemcitabine).	'In the context of the current application for the indications of relapsed or refractory HL or sALCL, brentuximab vedotin is intended for use as monotherapy and is not intended for use with other chemotherapeutic agents. The sponsor's experience with the combination use of brentuximab vedotin to date is thus summarized below for informational purposes only and applies to treatment settings other than relapsed or refractory HL or sALCL. The combination of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) and brentuximab vedotin was explored in patients with advanced-stage, newly diagnosed HL in completed Study SGN35-009. In this study, pulmonary toxicity was observed with the concomitant use of bleomycin, leading to its contraindication in combination with brentuximab vedotin. The study was amended to continue with the combination of doxorubicin, vinblastine, and dacarbazine (AVD) and brentuximab vedotin, and further instances of pulmonary toxicity were not observed. The combination of AVD and brentuximab vedotin is currently being explored versus ABVD alone in randomized Phase III Study C25003; the primary endpoint is modified progression-free survival (PFS), and study completion is anticipated in 2018.	The planned or ongoing studies are considered acceptable. The sponsor should provide interim and final study reports in PSUR updates, when they become available. It is noted that Clinical Trial NCT01780662 investigates a combination of brentuximab and gemcitabine. This should be added to the pharmacovigilance plan. The sponsor should add the studies NCT01780662,

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	OPR evaluator's comment
		C25003, SGN35-011, SGN35-014, and X25001 to the pharmacovigilance plan and assign them to a new Ongoing Safety Concern (Interaction with other anticancer agents). Furthermore, the sponsor should use the results of the interaction studies to update the 'Interaction with other Medicines' section, when the results become available. (cont'd)
	Findings of ongoing Phase I Study SGN35-011, an open-label, 3-arm study exploring combinations of brentuximab vedotin with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or cyclophosphamide, doxorubicin, and prednisone (CH-P) in patients with treatment-naïve CD30+ mature T-cell and NK cell neoplasms, led to the selection of brentuximab vedotin in combination with CH-P as a regimen for further study. Study SGN35-014 in patients with mature T-cell lymphoma is a randomized, double-blind, Phase III study of brentuximab vedotin in combination with CH-P versus CHOP in patients with treatment-naïve CD30+ mature T-cell lymphomas. This recently initiated study uses a PFS primary endpoint and is anticipated to complete in 2017. Due to the aforementioned contraindication against the combination use of brentuximab vedotin and bleomycin, combination use with bleomycin-containing BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) regimens, escalated or otherwise, is not planned. Study X25001, a randomized, Phase II, investigator-initiated study, is currently being conducted by the German Hodgkin Study Group to explore combinations of brentuximab vedotin with modified BEACOPP regimens versus escalated BEACOPP. Two experimental regimens are under investigation: (1) brentuximab vedotin plus etoposide, Adriamycin , cyclophosphamide, procarbazine, and prednisone (BrECAPP), and (2) brentuximab vedotin plus etoposide, Adriamycin , cyclophosphamide, dacarbazine, and dexamethasone (BrECADD).'	The sponsor's statement that brentuximab is indicated as monotherapy, that is not with concomitant use of other anti-cancer drugs is not sufficiently displayed in the proposed PI and off-label use as a combination drug is likely to occur. As a result, 'Interaction with other anticancer agents' needs to be added as an Ongoing Safety Concern and appropriate PI changes need to be made: In the 'Indications' section, the PI should clearly state that brentuximab is indicated as monotherapy only (or a statement to that effect).

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	OPR evaluator's comment
		In the 'Interaction with other Medicines' section, the PI should clearly state that brentuximab cannot be used concomitantly with other anticancer agents (or a statement to that effect).
In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft product information document be revised as follows: In the 'Precautions' section, the PI should have a separate entry for use in renal impairment and use in hepatic impairment.	'The sponsor accepts the evaluator's recommendation, and the entries for renal and hepatic impairment in the Precautions section have been separated as requested.'	This is considered acceptable.
In the 'Precautions' section, under 'Use in renal impairment', the PI should include a statement that describes the effect of severe renal impairment on MMAE clearance.	'The sponsor accepts the evaluator's recommendation, and the text within the 'Precautions - Use in Renal Impairment' heading has been revised to include a statement that describes the effect of severe renal impairment on MMAE clearance.'	This is considered acceptable.
In the 'Precautions' section, under 'Use in hepatic impairment', the PI should include a statement that describes the findings of liver toxicity in non-clinical studies with rats.	'Please be advised that data from patients with renal and hepatic impairment are currently under review. Information regarding use in special populations will be updated in the appropriate sections of the PI following completion of this evaluation. In the interim, the sponsor accepts the evaluators recommendation, and the text within the 'Precautions – Use in Hepatic Impairment' heading has been updated with the nonclinical findings accordingly.'	This is considered acceptable.
In the 'Interaction with other Medicines' section, the PI should state that the combined use of brentuximab vedotin and bleomycin is associated with pulmonary toxicity and therefore contraindicated, even though this statement is already found in the 'Contraindications' section (or a statement to that effect).	'The sponsor accepts the evaluator's recommendation, and the 'Interactions with other Medicines' section has been updated with the following statement: The combined use of Adcetris and bleomycin is associated with pulmonary toxicity and is therefore contraindicated (see 'Contraindications').'	This is considered acceptable.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	OPR evaluator's comment
In the 'Interaction with other Medicines' section, the PI should contain a statement of potential or definite interactions of brentuximab with other common cancer drugs (or absence thereof, or missing information if no data is available) (in particular with regard to drugs of the ABVD, CHOP, or BEACOPP escalated regimens, or gemcitabine) (or a statement to that effect).	'The sponsor accepts the evaluator's recommendation, and the 'Interactions with other Medicines' section has been updated with the following statement: There are no drug-drug interactions data available with other chemotherapy regimens.'	This is considered acceptable. The sponsor should use the results of the interaction studies and other information to update the 'Interaction with other Medicines' section, when new information becomes available.

VI. Overall conclusion and risk/benefit assessment

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

Introduction

The mechanism of action of Adcetris is portrayed as the targeting of CD30-expressing cells, internalisation of the ADC, traffic to the lysosomal compartment and release of MMAE via proteolytic cleavage. MMAE is considered to be the primary mediator of cytotoxicity. The Non-Clinical Evaluation Report notes minimal antibody-dependent cellular cytotoxicity and no evidence of complement-dependent cytotoxicity. Several clinical studies of other, unconjugated anti-CD30 antibodies in HL showed low efficacy.[10]

After intracellular release, free MMAE appears extracellularly over time. It is possible some release of MMAE occurs independently of CD30-mediated internalisation.

CD30 is a member of the tumour necrosis factor receptor (TNFR) superfamily; it signals via NF-κB.[11] CD30 is expressed on some activated T and B cells and eosinophils in healthy subjects. The role of the CD30-CD30L path in immunity is not understood.[12] Recent data imply a role for CD30 signalling in the immune response to mycobacteria.[13]

Soluble CD30 is detectable in healthy subjects' serum and may be elevated in pathology.

There is evidence that other lymphomas express CD30.[14]

Quality

Outstanding GMP issues need to be resolved prior to registration.

Other issues included:

- Shelf life;

[10] Forero-Torres et al (SGN-30), 2009; Ansell et al 2007 (MDX-060)
[11] Wright and Duckett, 2009.
[12] Kennedy et al 2006.
[13] Guo et al 2013, Infection and Immunity.
[14] Sabattini et al 2013.

- Ratio of free MMAE to ADC in clinical studies; and
- Basis for dose capping at 100 kg.

Pharmaceutical Subcommittee (PSC) recommendations concerning use in hepatic and renal impairment resulted in revised Product Information text.

A proposed condition of registration relates to batch release testing. It is also noted that Adcetris will be initially suppled in an EU carton and vial (with an Australian over sticker) and as such, does not fully comply with the Australian labelling standard. It is recommended that a Section 14 exemption to supply goods that do not comply with the labelling standard Therapeutic Goods Order 69 should be issued on or after the time of registration.

Nonclinical

The non-clinical evaluator had no objections to registration.

Pregnancy Category D is recommended. CD30 may be expressed on decidual cells in the pregnant uterus.

Clinical

There were six clinical studies, and a population PK study.

Table 5. Overview of Clinical Studies

Study ID	Description	Comment
SG035-0001	Phase I dose escalation in relapsed or refractory CD30+ malignancy. First time in human. 45 subjects (42 out of 45 HL); 12 out of 45 received 1.8 mg/kg three weekly.	Contains PK and anti-tumour activity data
SG035-0002	Phase I dose escalation in relapsed or refractory CD30+ malignancy. 44 subjects (38 out of 44 HL). Highest dose was 1.4 mg/kg; given weekly for 3 weeks per 4 week cycle.	Contains PK and anti-tumour activity data
SG035-0003	Phase II, single arm study in relapsed or refractory HL post-ASCT. See Younes et al, 2012.	Pivotal; sparse PK sampling
SG035-0004	Phase II, single arm study in relapsed or refractory sALCL. See Pro et al, 2012.	Pivotal; sparse PK sampling
SGN35-007	Phase I QT study. 52 subjects with CD30+ malignancy (49 out of 52 with HL).	QT assessment
SGN35-008a	Phase I drug interaction/PK study. 56 subjects with CD30+ malignancy (40 out of 56 had HL).	Contains PK data

Results from Study SGN35-008b (hepatic, renal impairment) were submitted late and were not considered by the clinical evaluator. They were considered by the Delegate.

Ongoing studies include:

- Study 005, a Phase III, placebo-controlled study in HL (high risk post ASCT);
- Study C25001, a Phase III non-randomised study in CD30+ mycosis fungoides or primary cutaneous anaplastic large cell lymphoma (pcALCL); and
- Study 009, a Phase I study in treatment-naive HL.

Pharmacokinetics (PK)

Three analytes were measured to assess the product's PK profile:

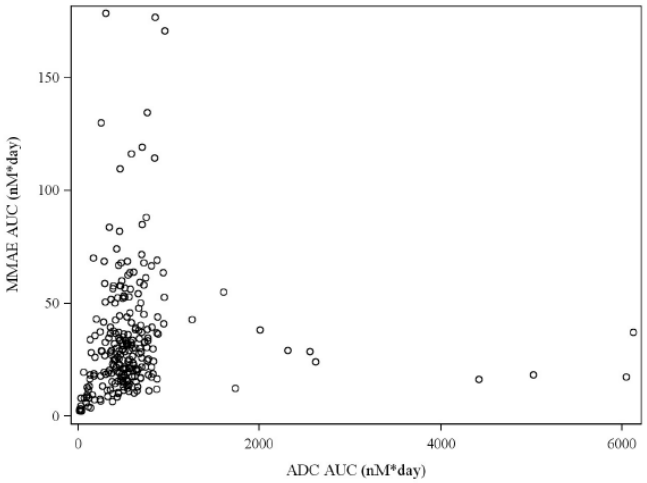
- brentuximab vedotin (the antibody drug conjugate);

- MMAE (released small molecule); and
- total antibody (brentuximab vedotin + cAC10).

Time to maximum concentration (T_{max}) for the ADC was immediately after end of infusion; MMAE's T_{max} was 2 days after dosing at 1.8 mg/kg.

There was a modest correlation between ADC area under the curve (AUC) and MMAE AUC that tended to break down at high values, as per the following scatter-plot derived from Studies 0001-0004:

Figure 4. Scatter-plot for ADC AUC and MMAE AUC



This translated into a mean value across analysed study subjects (in the intention to treat (ITT) population; n = 249) for the ratio (AUC MMAE is to AUC ADC) of 0.079, with a range 0.003 to 0.587. A quarter of subjects had a ratio of 0.103 or higher.

The ADC had a terminal half-life of 4 to 6 days, with steady state by Cycle 2, no observed accumulation and a volume of distribution approximately 8 to 10 litres (that is limited distribution beyond the vascular space, consistent with distribution of other mAbs). MMAE's apparent terminal half-life was approximately 4 days at the 1.8 mg/kg dose level, with steady state by Cycle 2 and 20 to 50% decreased exposure relative to the initial dose, at Cycles 2 to 3; rat studies with IV MMAE indicated wide tissue distribution.

The primary route of MMAE excretion was faecal (72%) with some urinary excretion (28%); intact MMAE was the main species. This was based on a study where only 24% of total MMAE was recovered (over 1 week), either because of retention in plasma (consistent with calculated half-life) or because of metabolism to moieties not captured/accounted for. It is estimated that less than or equal to 1.5% of circulating MMAE is MMAE transferred to other proteins via maleimide transfer. MMAE clearance was halved in patients with low serum albumin.

Renal and hepatic impairment

The sponsor supplied new information to the TGA on 14 October 2013 regarding use in hepatic and renal impairment. The clinical evaluator has not considered this new information; it is considered by the Delegate here.

SGN035-008 Part B

An addendum to the Clinical Overview uses available data from Study SGN035-008 Part B (PK of brentuximab vedotin in patients with CD30+ lymphomas and hepatic or renal impairment). This data were outlined in a document called "Hepatic or Renal Impairment

Report – Safety" also known as "Interim Report Regarding MEA-001 (Hepatic or Renal Impairment)" and dated 9 October 2013.

In the study, a starting dose of 1.2 mg/kg was used; a 100 kg cap was used. The study was open-label and non-randomised.

10 patients with renal impairment were enrolled in SG035-008 Part B. Mild renal impairment was defined as Creatinine Clearance (CrCl) greater than 50 and up to 80 mL/min; moderate, 30 to 50 mL/min and severe, less than 30 mL/min. Apparently no dialysis patients were studied. 9 patients had complete PK outcomes.

The comparison was with patients with normal organ function enrolled in SGN-008A (drug interaction study; also 1.2 mg/kg). The clearest finding was an increase in MMAE exposure in severe renal impairment. Also relevant given the proposal to reduce starting dose to 1.2 mg/kg in the absence of direct efficacy data, the reduction in ADC exposure in those with severe impairment was not 'extreme' and there was no trend across the worsening categories of renal impairment.

One patient had a fatal adverse event (AE) that was considered considered unrelated. 1 patient had a Grade 4 episode of hypokalaemia considered related to treatment.

Pivotal Phase II studies

Patients with mild or moderate renal impairment (based on Glomerular Filtration Rate (GFR)) could enrol in the pivotal Phase II studies (starting dose 1.8 mg/kg) and it was claimed these patients had no appreciably altered safety profile compared with patients with normal renal function (but see below). Therefore, the sponsor's recommendation to commence at 1.2 mg/kg applies only to patients with severe renal impairment.

Table 6. Studies SG035-0003 and SG035-0004: Stages of Renal Impairment per calculated Glomerular Filtration Rate

Stage of Renal Disease	GFR (mL/min/1.73m^2)	Number of Patients with Renal Impairment	
		Study SG035-0003 n=23*	Study SG035-0004 n=22*
1 (Normal)	≥90	--	--
2	60-89	18	14
3	30-59	5	7
4	15-29	0	1
5	<15	0	0

GFR = glomerular filtration rate

*Analysis includes only patients with baseline GFR indicative of renal impairment.

In Study 0003, dose reductions were recorded for 2 out of 23 with renal impairment and 9 out of 79 without (a similar fraction) but in Study 004 with lower overall numbers there was some discordance, with dose reductions recorded for 5 out of 22 with renal impairment and 2 out of 36 without (23% versus 6%).

Sub-group analysis of AEs by renal function was consistent with an increased incidence of AEs such as peripheral neuropathy and neutropenia with worsening renal function, however sample size was limited and these links have not been established definitively.

Hepatic impairment data

SGN035-008 Part B

Seven patients with hepatic impairment (Child-Pugh 5-15[15]) were enrolled, some with Eastern Cooperative Oncology Group Performance Standard (ECOG PS) 3; 3 patients died (2 deaths were due to fungal infection) and one patient discontinued due to steatohepatitis thought related to Adcetris by the investigator.

Complete PK data were available for 3 patients and incomplete data were available for 4 further patients. 'Mathematical imputation' was applied to PK data from these 4 further patients. Comparison of PK outcomes from the 'complete PK profile' set and the whole group of 7 did not reveal large differences.

Table 7. Data from the "complete PK profile" set

	Mild Hepatic Impairment	Moderate Hepatic Impairment	Severe Hepatic Impairment	All Patients
PK Parameter	**Ratio of GM (90% CI)**	**Ratio of GM (90% CI)**	**Ratio of GM (90% CI)**	**Ratio of GM (90% CI)**
ADC				
$AUC_{0-\infty}$	n = 1 0.57	n = 2 0.71 (0.54, 0.93)	n = 0 -	n = 3 0.66 (0.53, 0.83)
C_{max}	n = 1 0.88	n = 5 0.81 (0.63, 1.05)	n = 1 0.80	n = 7 0.82 (0.66, 1.01)
MMAE				
$AUC_{0-\infty}$	n = 1 3.51	n = 2 2.09 (0.78, 5.62)	n = 0 -	n = 3 2.48 (1.11, 5.56)
C_{max}	n = 1 2.79	n = 5 1.63 (0.87, 3.05)	n = 1 1.21	n = 7 1.68 (0.98, 2.89)

Run date: 08 August 2013

AUC0-∞ = Area under the concentration-time curve extrapolated to infinity; CI = confidence interval; Cmax = maximum observed concentration; GM = geometric mean

Concentration data from patients with normal organ function enrolled in Arm A-ket of the same study were used to calculate the geometric mean ratios. Samples from time points after brentuximab vedotin dosing (1.2 mg/kg) but before receipt of ketoconazole were used.

Safety assessment was confounded by co-morbidity. There were no data from the Pivotal Phase II studies.

Conclusions

Data from SGN035-008 Part B are 'top line results' and have not been considered by the clinical evaluator.

Population PK analyses indicate ADC clearance appears to be affected by severe renal impairment (calculated CrCl less than 30 mL/min) while MMAE apparent clearance is affected by moderate (CrCl 30 to 50 mL/min) and severe renal impairment. Data from 008B are more compelling than population PK analysis, at least for renal impairment.

In severe renal impairment, benefit/risk appears worse than in patients with normal renal function, in that exposure to MMAE increases and, possibly, exposure to ADC decreases (the risk being that toxicity increases while efficacy decreases). While the

[15] The Child-Pugh score (sometimes the Child-Turcotte-Pugh score) is used to assess the prognosis of chronic liver disease, mainly cirrhosis.

recommendation to start at 1.2 mg/kg in severe renal impairment offsets the toxicity risk to some extent, it magnifies the risk of decreased efficacy. However, this decrease in efficacy is only relative to others on Adcetris, and the Delegate is prepared to accept the sponsor's position given that the population in question has limited treatment options.

In hepatic impairment, direct PK data were very limited and although an increase in MMAE exposure was seen overall, it was actually highest in the one patient with mild impairment and lowest in the one patient with severe impairment. These data are not very convincing as a basis for dosing recommendations and call into question the benefit-risk balance in patients with any hepatic impairment. Use at 1.8 mg/kg risks significantly elevated exposure to MMAE (in a setting where even 'normal' exposure to MMAE may link to clinically significant AEs such as peripheral neuropathy and, more consistently, neutropenia) while use at 1.2 mg/kg may still expose the patient to high MMAE levels AND is likely to decrease ADC exposure on two counts (33% lower dose in addition to observed PK effect on ADC levels) with consequent impacts on efficacy.

Earlier, it was noted that MMAE clearance was halved in patients with low serum albumin. While there are other causes of low albumin, the increased exposure in hepatic impairment could potentially be related to this factor.

The Delegate suggests modification to the PI data, details of which are beyond the scope of this AusPAR.

Drug interactions

Drug interactions were studied in vitro and pointed to MMAE being a substrate of CYP3A4 and P-glycoprotein (P-gp).

Table 8. Potential for interaction data from Study SGN35-008A

Drugs	Result	Interpretation
ADC and midazolam (CYP3A4 substrate) given at MMAE $_{Tmax}$	Midazolam exposure not greatly affected	ADC/MMAE do not induce or inhibit CYP3A4
ADC and rifampin (CYP3A4 and P-gp inducer)	ADC exposure not affected greatly. MMAE exposure halved.	MMAE is a substrate of CYP3A4 and/or P-gp.
ADC and ketoconazole (strong inhibitor of CYP3A4 and P-gp)	ADC exposure not affected greatly. MMAE exposure increased by 1.25-1.34-fold	MMAE is a substrate of CYP3A4 and/or P-gp

Dose

Dose is calculated per kg, capped at 100 kg. The sponsor notes:

> *'...even though the volume of distribution of these agents increases with total body weight, the per kilogram volume of distribution does not increase, leading to over-compensation for increasing body weight*[16] *and resulting in higher therapeutic agent AUC in the serum of heavier patients. The higher AUC under these circumstances is due to less vascularity per kg of body weight for patients who weighed more than 100 kg than for patients who weighed less than or equal to 100 kg.'*

The PSC gave advice regarding this argument, which was considered by the Delegate.

Despite this cap, MMAE exposure trended up with weight (for example MMAE AUC (µg.day/mL) 21.7 for less than or equal to 60 kg; 26.4 for greater than 60kg and up to 80 kg, 29.0 for over 80kg and up to 100 kg; and 34.5 for greater than 100 kg). This did not translate into obvious differences in AEs, even though there was a link between some AEs

[16] Fasanmade 2011

and MMAE exposure. There were no obvious differences in efficacy in those subjects weighing greater than 100 kg, relative to lighter subjects.

Pharmacodynamics (PD)

Anti- therapeutic antibody antibodies (ATAs)

In Phase II studies, 7% of subjects seroconverted to become persistently positive for ATAs, however there was no effect on PK parameters. There was a trend towards a higher incidence of infusion-related reactions in patients with persistent ATAs (27%) versus those with transient ATAs (12%) or those negative for ATAs (7%). Two patients with high titres discontinued due to infusion-related reactions, although 3 others with high titres completed 16 cycles of treatment. There was no apparent impact on efficacy.

Efficacy – Hodgkin lymphoma

Pivotal study – Study 0003

This was a Phase II, single arm, open label study. One hundred and two patients were enrolled. Patients had relapsed or refractory HL after high dose chemotherapy and ASCT. (Allogeneic hematopoietic stem cell transplantation (AlloSCT) was an exclusion.) Median age was 31 years (range 15 to 77 years) and ECOG PS was 0-1. Patients were required to have histologically proven CD30+ disease, Fluorodeoxyglucose (FDG) avid disease by positron emission tomography (PET) and measurable disease by spiral X-ray computed tomography (CT).

Patients had received a median of 3.5 prior systemic chemotherapy regimens. ABVD was the main choice for first line therapy (88 out of 102 patients); the most common second line therapy prior to ASCT was ICE[17] (35 out of 102). After failure of ASCT, radiotherapy was the commonest initial approach (32 out of 72).

Patients received brentuximab vedotin 1.8 mg/kg infused IV over 30 minutes every 3 weeks as a single agent. Median duration of treatment was 27 weeks (range 3-56).

The cut-off for analysis of objective response was 20 December 2010. The cut-off for analysis of some secondary endpoints was 1 August 2011. An efficacy update used a cut-off of 19 June 2013.

Overall response rate (ORR)

ORR was the primary endpoint; it was based on 'independent review facility' (IRF) assessment.

ORR was 75%, including 34 out of 102 (33%) who achieved a complete response and 42 out of 102 (41%) who achieved a partial response. There was good concordance with investigator assessment.

Median duration of objective response was 6.7 months (range 1.2+ to 26.1+ months). Median duration of complete response was not calculable (median not yet reached).

ORR was similar in patients with 0 versus 1+ treatments post ASCT. Of 9 patients with no prior objective response to therapy, 5 out of 9 had a complete response.

Progression-free survival (PFS)

Estimated PFS was 5.6 months. About 47% of subjects were progression-free at 6 months, 34% at 12 months and 23% at 24 months.

[17] Ifosfamide, carboplatin and etoposide.

In an efficacy update presented only as 'top-line results' in the PSUR, PFS was stratified by PET status as follows: median PFS of 4.8 months for patients PET+ at cycle 4; median PFS of 29.2 months for patients PET- at cycle 4. There was no breakdown of the PET+ versus PET- proportion.

Comparison of investigator-assessed PFS on Adcetris with PFS on most recent systemic therapy after ASCT was made. PFS was better for Adcetris (median 34 weeks) than most recent therapy after ASCT (median 18 weeks); the HR was 0.40 ($p < 0.001$). Such analyses are subject to significant biases, but the effect size is indicative of a probable advantage for Adcetris.

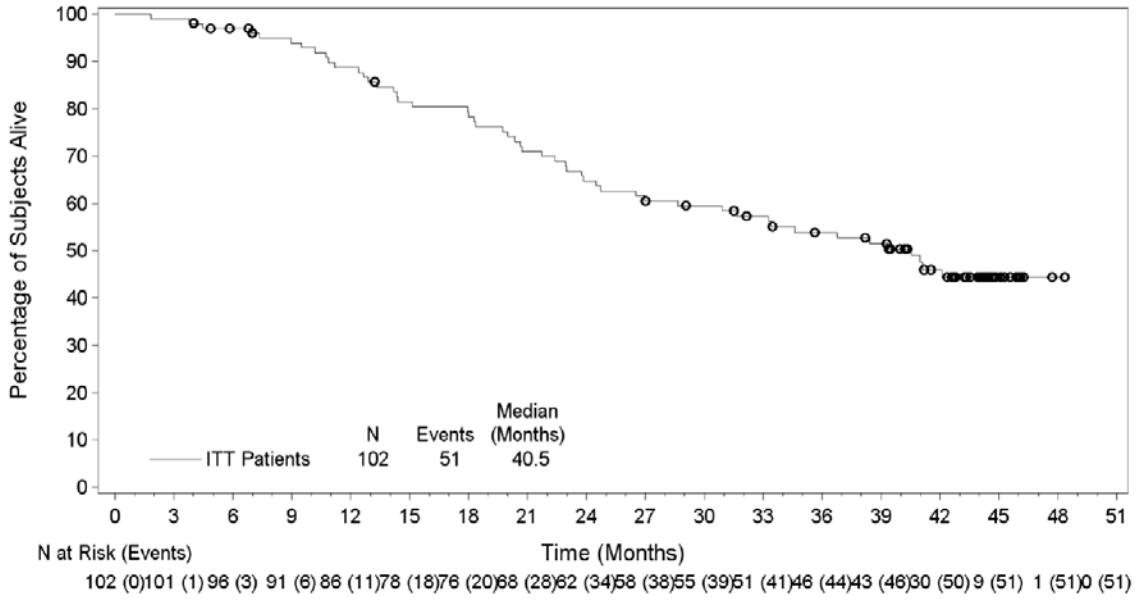
Comparison of PFS on Adcetris with PFS on most recent systemic therapy (including ASCT) was made; PFS was again better for Adcetris (39.1 weeks) than most recent therapy (26.6 weeks) (HR 0.52, $p < 0.001$).

Overall survival (OS)

Estimated median OS as of 1.8.2011 was 27 months. About 89% were alive at 12 months, and 61% at 24 months.

In an efficacy update (19 June 2013; ITT), median OS was 40.5 months and estimated 24 month survival was 65%.

Figure 5. The Kaplan Meier curve for OS



Quality of life

B symptom resolution was assessed. Twenty seven out of 35 patients with B symptoms at baseline had resolution of symptoms (median time to resolution was 3.1 weeks).

Other studies – 0001, 0002

In Study 0001, 42 out of 45 subjects had HL. 40% of HL patients attained an objective response (including 6 out of 12 given 1.8 mg/kg and 7 out of 10 given 2.7 mg/kg).

In Study 0002, no patients received 1.8 mg/kg. Twenty out of 38 HL patients had an objective response (including 10 out of 38 with a complete response, at doses as low as 0.8 mg/kg).

HL patients who have not received ASCT

In Studies 0001-0002, 20 HL patients had not received prior ASCT. ORR was 30% (not all patients received 1.8 mg/kg). Of the 6 responders, response durations were censored as ongoing at study closure after 6.8 to 13.8 months. The sponsor contends:

> *'These data suggest that clinical benefit with brentuximab vedotin is observed in relapsed or refractory HL in the absence of prior ASCT. As a fraction of patients with HL that has failed frontline therapy never achieve sufficient disease control to qualify for ASCT, demonstration of durable responses in these particularly high-risk patients provides evidence of direct clinical benefit that extends to this additional unmet need population.'*

The EMA's assessment of Adcetris considers 40 HL patients who had not received prior ASCT (and who were treated at 1.8 mg/kg three weekly), that is an additional 20 patients from sources other than Studies 0001-0002; in this larger population the ORR was 55% (including 22.5% CR, and also including 20% who went on to SCT). This larger dataset has not been seen by the TGA's Clinical Evaluator. Data about PFS and OS were insufficient in the larger dataset to draw conclusions, according to the EMA assessment.

Exposure-response

In Studies 0001 and 0002, the sponsor found a modest correlation between Cycle 1 ADC AUC and C_{max} and greatest tumour size percent reduction (Pearson's correlation co-efficient -0.33 to -0.41, looking at exposure versus percent change in tumour size). In Study 0001 (but not Study 0002), there was also correlation between MMAE AUC and C_{max} and greatest tumour size reduction.

Efficacy – sALCL

Pivotal study – Study 0004

This was a Phase II, single arm, open label study of single agent brentuximab vedotin in patients with relapsed or refractory sALCL. 58 patients were enrolled. Median age was 52 years (range, 14-76 years). 72% (42 out of 58) were anaplastic lymphoma kinase (ALK) negative, consistent with the poorer prognosis this infers across sALCL patients. Patients had received a median of 2 prior chemotherapies; 26% had received a prior ASCT (alloSCT was an exclusion). The sponsor further notes:

> *'Sixty-two percent of patients had primary refractory disease, defined as failure to achieve a CR with frontline therapy, or relapse within 3 months of frontline therapy. Relative to the most recent prior therapy, 50% of patients had a best response of stable disease or disease progression, and 50% of patients had disease that had progressed after a response of PR or CR. In addition, 22% of patients had never achieved an objective response with any prior therapy.'*

The dose used was 1.8 mg/kg infused IV over 30 minutes every 3 weeks. Median exposure was 23.5 weeks.

Overall response rate

This was the primary endpoint, based on independent review of best clinical response.

ORR was 86%, including 34 out of 58 (59%) with complete response and 28% with partial response. There was good concordance with investigator assessment (83% ORR).

Median duration of objective response was 13.2 months (range 0.1-21.7+ months); median duration of complete response had not been reached.

ALK status did not influence ORR (ALK+, 81%; ALK-, 88%). Other subgroup analyses revealed no major disparities.

The sponsor reports that:

> *'In the Phase II Population, both the median duration of response and the percentage of patients with a response for 1 year or more appeared to generally increase with ADC exposure, plateauing at higher exposure levels. No clear trend was observed for MMAE exposure.'*

Progression-free survival

Median duration of PFS was 14.3 months (with an estimated 65% progression-free at 6 months, 54% at 12 months and 37% at 24 months).

Comparison of investigator-assessed PFS on Adcetris with PFS on most recent prior therapy (with or without ASCT) was made. PFS was 14.5 months for Adcetris versus 5.9 months for prior systemic therapy (HR 0.44, $p < 0.001$). This strongly suggests a benefit of the ADC given that PFS might generally be expected to decline with each subsequent line of therapy.

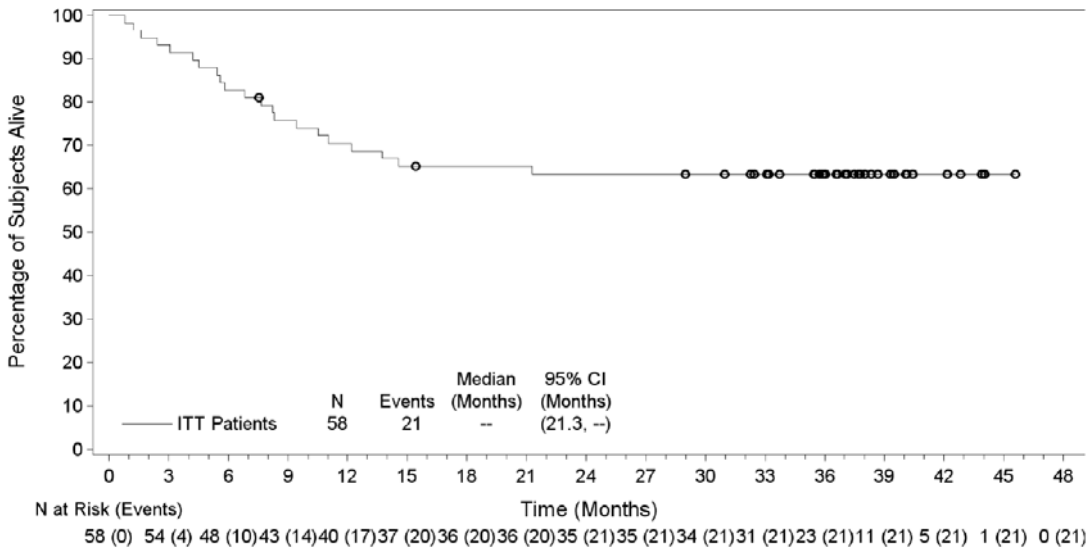
In an efficacy update, median duration of complete remission off treatment was 14.1 months.

Overall survival

Median OS had not been reached by data cut-off (13 July 2011); estimated survival at 6 months was 83% and at 12 months was 70%.

In an efficacy update (19 June 2013), median OS was still not reached and estimated OS at 24 months was 63%.

Figure 6. The Kaplan-Meier curve



Quality of life

B symptom resolution rate was 82% (14 out of 17), with median time to resolution of 3.14 weeks.

Other studies – 0001, 0002

In Study 0001, 2 out of 45 subjects had sALCL (one in the 1.2 mg/kg cohort, one in the 2.7 mg/kg cohort). In both patients, best clinical response was complete response.

In Study 0002, no patients received the proposed dose of 1.8 mg/kg. However, 4 out of 5 patients with sALCL had a best clinical response of complete response.

Safety

Exposure

Across the six clinical studies reported above, 357 patients received greater than or equal to 1 dose of Adcetris. Of these, 261 patients received greater than or equal to 1 dose of 1.8 mg/kg (160 in Phase II studies, 12 in Study 0001, 52 in Study 007 and 37 in Study 008A). The Phase II population (n = 160) was used to analyse various safety outcomes.

A Periodic Safety Update Report (19.8.2012-18.2.2013) was also reviewed; cumulative post-marketing exposure since first approval was approximately3690 patients worldwide (6663 if subjects in clinical trials and named patient programmes are included).

Overview of safety profile

Peripheral neuropathy is the main drug-related toxicity. Other significant adverse outcomes include neutropenia (sometimes with infection) and infusion-related reactions (including anaphylaxis). One in five treated subjects discontinued due to AEs.

Deaths and serious AEs

Six patients (6 out of 160; 4%) in the Phase II population died within 30 days of the last dose of Adcetris. Causes of death other than disease progression included acute myocardial infarction, acute renal failure, respiratory failure and sudden death. None of these deaths was attributed to the drug. Also, 49 out of 160 (31%) died during follow-up.

Across the 357 patients in the clinical programme, there were 2 reports of treatment-related deaths: one patient given 3.6 mg/kg died after febrile neutropenia and presumed septic shock; one patient died after pancytopenia, cytomegalovirus (CMV) infection and intracranial haemorrhage.

Serious AEs were reported in 50 out of 160 patients in the Phase II population (31%). 16% had an SAE considered related to Adcetris. Commoner SAEs other than disease progression were: abdominal pain; demyelinating polyneuropathy; pulmonary embolism; and septic shock.

Discontinuations due to AEs

AEs leading to discontinuation were seen in 36 out of 160 patients in the Phase II population (23%). Peripheral neuropathy (10%) and neutropenia were the commonest AEs.

Dose modifications due to AEs

AEs leading to dose modification were seen in 79 out of 160 (49%) in the Phase II population. Peripheral neuropathy was the commonest cause.

Common AEs

Common AEs in the Phase II population included: peripheral sensory neuropathy (45%); fatigue (43%); nausea (41%); diarrhoea (34%); pyrexia (31%); URTI (31%); neutropenia (21%) and vomiting (20%).

Grade greater than or equal to 3 AEs (that is at least 'severe') were reported in 58% and included neutropenia, peripheral sensory neuropathy, thrombocytopenia and anaemia. Grade 4 (life-threatening) AEs occurred in 23 out of 160 patients in the Phase II population; neutropenia (n = 11) and thrombocytopenia (n = 5) were prominent.

AEs of interest

Peripheral neuropathy

MMAE is a tubulin inhibitor; peripheral neuropathy is a toxicity of microtubule-targeting agents. CD30 expression on nervous tissue is not reported, so the peripheral neuropathy

seen with Adcetris might be due to free MMAE. Another explanation is implied by reported homology between the extracellular domain of CD30 and the nerve growth factor receptor family.[18] However, the NCER did not note any cross-reactivity to neural tissue/nerves.

In Study 0002, weekly dosing (for 3 weeks per 4 week cycle) over months resulted in peripheral neuropathy in three-quarters of subjects. The frequency of this AE was apparently lower with 3-weekly dosing.

In the Phase II population, about half of subjects reported peripheral neuropathy. This was usually mild or moderate in severity. Twenty one out of 160 patients (13%) reported severe peripheral neuropathy; there were no Grade 4 events.

Table 9.

	HL (N =102) n (%)		ALCL (N = 58) n (%)		Total Ph 2 (N = 160) n (%)	
	Grade		Grade		Grade	
	Any	3	Any	3	Any	3
Any Peripheral Neuropathy SMQ AE	56 (55)	11 (11)	33 (57)	10 (17)	89 (56)	21 (13)
Peripheral sensory neuropathy	48 (47)	9 (9)[a]	24 (41)	7 (12)	72 (45)	16 (10)
Peripheral motor neuropathy	12 (12)	1 (1)	3 (5)	2 (3)	15 (9)	3 (2)
Paraesthesia	4 (4)	0	5 (9)	0	9 (6)	0
Demyelinating polyneuropathy	2 (2)	2 (2)	1 (2)	1 (2)	3 (2)	3 (2)
Neuralgia	0	0	3 (5)	1 (2)	3 (2)	1 (1)
Hypoaesthesia	2 (2)	0	0	0	2 (1)	0
Muscular weakness	2 (2)	1 (1)	0	0	2 (1)	1 (1)
Burning sensation	0	0	1 (2)	0	1 (1)	0
Gait disturbance	1 (1)	0	0	0	1 (1)	0
Nerve conduction studies abnormal	1 (1)	0	0	0	1 (1)	0
Polyneuropathy	0	0	1 (2)	1 (2)	1 (1)	1 (1)

Source: m2.7.4, Table 7.2.8.4.

Abbreviations: SMQ = Standardized MedDRA query.

The SG035-0003 CSR reports 8 patients (8%) with peripheral sensory neuropathy of maximum severity ≥ Grade 3. One patient had a grade change to 3 after the data cut for the CSR.

A distal to proximal pattern of development was mentioned. The sponsor drew comparisons with the neuropathy seen with microtubule inhibitors such as paclitaxel and docetaxel. Median time to onset was 12.4 weeks; higher grades occurred in later treatment cycles, and the sponsor states onset of motor neuropathy was later than non-motor events. The AE was usually reversible (median time from onset to resolution or improvement was 16 weeks); no repeat nerve conduction studies were reported. 18% of patients required dose modification due to peripheral neuropathy. Discontinuation due to this AE occurred in 12% of the Phase II study population.

Neutropenia and infection

Grade 3 neutropenia occurred in 14% of the Phase II population; Grade 4 neutropenia occurred in 7%. Median duration was one week. There was no major impact on dosing. No patients discontinued due to infection; there were no fatal infections. The sponsor writes:

> *'Based on analyses of the combined data from Phase I and pivotal Phase II studies (SG035-0001, SG035-0002, SG035-0003 and SG035-0004), there was an apparent trend in the relationship between both the AUC and* C_{max} *for MMAE and grade of*

[18] Durkop et al 1992

> *treatment-emergent neutropenia. Median AUC and* C_{max} *were generally higher in patients experiencing higher grades of treatment-emergent neutropenia.'*

Thirty nine Phase II subjects (24%) had the laboratory finding of Grade 3-4 lymphopenia; 3 of these patients had a temporally related infection.

Infections were see in 61% of Phase II subjects but most were mild or moderate. URTI predominated. Serious infections were reported in 10% but no pattern was observed (herpes zoster was reported in 8 out of 160, including disseminated cases). This population is susceptible to infection for various reasons, for example incomplete immune reconstitution after ASCT; active disease; previous chemotherapy; et cetera. 14 patients (9%) had infection associated with Grade 3+ neutropenia, that is 39% of patients with Grade 3+ neutropenia had an associated infection. Febrile neutropenia was not reported in Phase II studies.

In Phase I studies, several patients had significant CMV reactivation; both patients had been treated with allogeneic stem cell transplant.

Infusion reactions including anaphylaxis

These occurred in approximately11% in Phase II studies; few were severe; most occurred in cycles 1-2. There were two diagnoses of anaphylaxis in Phase I studies, however most infusion reactions were manageable with infusion interruption, allowing completion of the dose and ongoing treatment (+/- prophylaxis). There was a link to ATAs (see above).

Serious skin reactions

There was one report of Stevens Johnson syndrome in the Phase I-II studies, leading to treatment discontinuation. A single case of toxic epidermal necrolysis (TEN) was reported in the PSUR.

Pancreatitis

The sponsor has supplied new but limited information concerning pancreatitis:

> 'Acute pancreatitis has been observed in patients treated with Adcetris. Fatal outcomes have been reported.'

PML

There have been two reports of confirmed progressive multifocal leukoencephalopathy (PML), and one suspected case. Three new cases were reported in the PSUR. PML is reported in post-transplant patients at a frequency of approximately1.24 per 1000 person-years. The US PI has a black-box warning about PML.

Other

There was a report of tumour lysis syndrome. Hyperglycaemia was reported in 6% of patients. Study 007 found no cardiac ventricular repolarisation risk for Adcetris.

One study ("009") suggested an increased rate of pulmonary toxicity in patients receiving bleomycin + Adcetris; there was one fatal case. The sponsor has proposed to contraindicate use of these two agents. An interaction was observed in an earlier study of SGN-30 (an unconjugated anti-CD30) and gemcitabine/vinorelbine/Caelyx, where average exposure to monoclonal antibody (mAb) was about 10-fold higher than for Adcetris.[19] There, 5 out of 23 patients developed Grade 3-5 pneumonitis and all had a V/F FcγRIIIa gene polymorphism. It was postulated this was due to exacerbation of gemcitabine-induced toxicity, but there was no formal demonstration of this.

[19] Blum et al 2010.

Exposure-response

The sponsor noted that:

> *'In general, in the three weekly population, patients with lower exposures were less likely to experience an AE greater than or equal to Grade 3 over time. Based on the results from 2 different statistical models, MMAE AUC appears to be the most important PK-based factor in the incidence of Grade 3 or higher AEs.'*

The relationship between drug exposure and frequency of diarrhoea, neutropenia and peripheral neuropathy was explored. No relationship was seen for diarrhoea.

A relationship was suggested for neutropenia and ADC AUC, and also for neutropenia and MMAE AUC and C_{max}, as follows:

Table 10. Median ADC and MMAE Exposure by Highest Grade of Treatment-emergent Neutropenia: Studies SG035-0001, SG035-0002, SG035-0003, and SG035-0004

		Median AUC (nM*day)		Median Cmax (nM)	
Neutropenia Grade	N	ADC	MMAE	ADC	MMAE
0	199	490.63	25.32	212.59	3.23
1	0	--	--	--	--
2	11	597.04	27.50	257.93	3.01
3	27	565.54	31.96	237.51	4.00
4	12	604.73	40.51	227.64	4.64

Source: Section 2.7.2.5, Figures 5.9, 5.10, 5.11, and 5.12.

Abbreviations: ADC = antibody-drug candidate; AUC = area under the concentration-time curve; MMAE = monomethyl auristatin E.

Patients not experiencing treatment-emergent neutropenia are in the Grade 0 category.

Neutrophils are not recognised as expressing CD30. It is possible that neutropenia is related to free MMAE exposure.

A relationship was suggested for peripheral neuropathy and ADC AUC and C_{max} (but not MMAE exposure), as shown below:

Table 12 Median ADC and MMAE Exposure by Highest Grade of Treatment-emergent Peripheral Neuropathy: Studies SG035-0001, SG035-0002, SG035-0003, and SG035-0004

		Median AUC (nM*day)		Median Cmax (nM)	
Peripheral Neuropathy Grade (NCI CTC)	N	ADC	MMAE	ADC	MMAE
0	117	459.00	30.08	213.53	4.05
1	63	507.46	26.81	214.76	3.05
2	44	583.48	24.70	227.00	2.77
3	25	586.42	29.05	230.61	3.33
4	0	--	--	--	--

Source: Section 2.7.2.5, Figures 5.17, 5.18, 5.19, and 5.20.

Abbreviations: ADC = antibody-drug conjugate; AUC = area under the concentration-time curve; C_{max} = maximum plasma concentration; CTC = Common Terminology Criteria; MMAE = monomethyl auristatin E; NCI = National Cancer Institute; SMQ = standardized MedDRA query.

Subjects not experiencing treatment-emergent peripheral neuropathy SMQ are in the Grade 0 category.

Clinical evaluator's recommendation

The clinical evaluator concluded that there was *'strong favour for benefit over risk for the use of Adcetris for patients with far advanced stage Hodgkin's lymphoma and sALCL*'. The evaluator recommended accepting the sponsor's proposed indications. This view was confirmed in the Round 2 report.

Risk management plan

The RMP proposed by the sponsor was considered generally acceptable by the TGA. Some matters related to the content of the RMP, for example potential risks or important missing information to be included, remain unresolved (see RMP Round 2) but are not obstacles to registration. The sponsor should continue dialogue with the RMP Evaluation section to resolve these issues.

The RMP Evaluator recommends the following RMP-related condition of registration:

- Implement EU European Union Risk Management Plan (EU-RMP) Version 2.0 (dated 17 April 2013, DLP 18 February 2013) and Australian-Specific Annex Version 2.0 (dated July 2013), and any future updates as a condition of registration.

Attention is drawn to advice given to the RMP Evaluator by the Advisory Committee on Safety of Medicines.

Risk-benefit analysis

Delegate's considerations

Lack of Phase III studies

The two pivotal studies were Phase II, single agent studies. The sponsor notes that both relapsed/refractory HL and sALCL are rare conditions that lack specifically approved therapies and consistent standards of care.

Without randomised trials using appropriate comparators, it is difficult to be sure that benefit-risk is positive relative to current 'standard of care' (as diffuse as that may be). Nevertheless, objective response rates were high in HL and sALCL patients who had failed other therapies, and the high ORRs were complemented by promising PFS and OS data. 'Intrapatient' comparisons of PFS were made (Adcetris versus prior therapies), and these analyses supported the efficacy of Adcetris in both HL and sALCL.

Choice of primary endpoint

The primary endpoint in the pivotal studies was objective response rate (ORR). This is not endorsed as an appropriate primary endpoint in the TGA-adopted EU guideline on anticancer medicines, mainly because an objective response does not indicate (directly) clinical benefit. On the other hand, PFS and OS results were also reported and raised no concern that the benefit conferred by observed high ORR rates may be offset by toxicity or subsequent loss of activity.

Duration of treatment

The data seen to date support only up to 12 months of use. The sponsor may wish to explain within the pre Advisory Committee on Prescription Medicines (pre-ACPM) response (without introduction of new data requiring clinical evaluation) the change in the US PI that allows ongoing use. If data requiring substantial evaluation are required to explain the ongoing use of Adcetris, it would be more appropriate to submit a separate variation once the product is registered.

Use in hepatic impairment

The Delegate does not think there is sufficient evidence of positive benefit – risk balance in patients with any degree of hepatic impairment.

Indication

Evidence for positive benefit-risk balance in the HL subset with relapsed/refractory disease "following at least two prior therapies where ASCT or multi-agent chemotherapy is not a treatment option" is much weaker than evidence in the subset with relapsed/refractory disease "following autologous stem cell transplant (ASCT)", since the pivotal Phase II study only enrolled patients who had received prior ASCT. Nevertheless, Phase I study outcomes supported the former subset, and an analysis of additional patients in this subset by the EMA in no way undermined conclusions reached from looking at the Phase I data.

It is noted that the indications in HL and sALCL do not specify tumour positivity for CD30. This aligns with the US but not the EU approach for HL, and aligns with both US and EU approaches for sALCL.

Benefit versus risk

The main benefit offered by Adcetris in the targeted difficult-to-treat populations is the possibility of a durable, complete response translating to improved survival. A durable, complete response was seen in a reasonable proportion of subjects in Phase II studies. The most significant common toxicity was peripheral neuropathy, which may detract from quality of life and may require discontinuation from treatment. There were rarer, more serious AEs, for example anaphylaxis; Stevens Johnson syndrome (SJS)/TEN; possibly PML (the signal for this latter AE was difficult to distinguish from baseline).

Proposed action

The Delegate supports approval of Adcetris with the following very slightly modified indication:

> *Treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL):*
>
> - *Following autologous stem cell transplant (ASCT) or*
> - *Following at least two prior therapies where ASCT or multi-agent chemotherapy is not a treatment option.*
>
> *Treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL).*

Request for ACPM advice

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

- Is evidence from Phase II, uncontrolled studies sufficient to proceed with registration?
- In what patient population(s) does the ACPM see a positive benefit – risk balance for use of Adcetris?
- Should use be recommended in patients with hepatic impairment?

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

The application under consideration seeks registration of Adcetris (brentuximab vedotin) 50 mg Powder for Injection (for intravenous infusion) for the treatment of relapsed or refractory Hodgkin Lymphoma (HL) or systemic Anaplastic Large Cell Lymphoma (sALCL). Adcetris is an antibody-drug conjugate (ADC) that delivers an antineoplastic agent that results in apoptotic cell death in CD30-expressing tumour cells. HL is a rare haematological disease that has an excellent prognosis with frontline treatment in patients who present with early stages of disease. For those patients with primary refractory disease, who fail to experience a complete response with second-line treatments, are not candidates for autologous stem cell transplant (ASCT), and/or those who relapse following ASCT, no therapies have been shown to be effective. Similarly, sALCL is a very rare, aggressive lymphoma in which approximately half of patients develop treatment-resistant recurrent disease. Both patient populations intended for treatment with Adcetris therefore represent patients with a high unmet clinical need in Australia.

In the request for ACPM advice the Delegate proposes approval of Adcetris with a slightly modified indication, which includes the qualifier of 'CD 30+' for the HL component of the proposed indication.

Takeda accept this recommendation and hereby confirm that the proposed Adcetris indications for Australia are:

> Treatment of adult patients with relapsed or refractory CD30+ Hodgkin Lymphoma (HL):
>
> - Following autologous stem cell transplant (ASCT) or
> - Following at least two prior therapies where ASCT or multi-agent chemotherapy is not a treatment option.
>
> Treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma.

Sponsor's comment

The benefit risk profile of Adcetris

The clinical benefit of Adcetris has been studied in the setting of CD30+ malignancies as part of an extensive clinical development program. This program includes two of the largest Phase II single-arm studies performed in patients with relapsed or refractory HL (Study SG035-0003) or sALCL (Study SG035-0004). These studies provided compelling evidence of clinical benefit consisting of objective responses in more than 75% of patients rigorously assessed by an independent review facility (IRF), a high percentage of complete remissions (CRs; 33% in HL; 59% in sALCL), prolonged durations of response (greater than 6 months) and resolution of B symptoms in a substantial proportion of patients (greater than 75% where this condition was present at baseline prior to treatment with brentuximab vedotin. Whilst the limitations of the trial design are acknowledged, these are deemed acceptable in this instance due to:

- The rarity of the proposed indications – both relapsed or refractory HL and sALCL are designated as orphan products,
- The lack of an approved standard of care for use as a comparator,
- Independent clinical studies across two rare CD30+ diseases yielding mutually supporting data, and
- The high level of activity of Adcetris, including durable complete remissions (CR) and OS. As noted by the Delegate, the high objective response rates in HL and sALCL patients who had failed other therapies and the high CR rates were further

complemented by progression-free survival (PFS) and overall survival (OS) data and 'intra-patient' comparisons of PFS (Adcetris versus prior therapies), thereby collectively supporting the use of Adcetris for the proposed indications.

The compelling results of the Phase II data from two pivotal studies have supported the approval of Adcetris by several regulatory authorities and to date, Adcetris has been approved in 36 countries (as of 11 November 2013) including the US (2011), the EU via the centralised process (2012), Switzerland (2013) and Canada (2013). In addition, overall, the cumulative estimated patient exposure to Adcetris as of 18 August 2013 had reached 8726 patients, including 1527 patients from company- and investigator-sponsored clinical trials, 2119 patients from other initiatives such as the Named Patient, Special Access and Compassionate Use programs, and approximately 5080 patients from the post-marketing setting.[20]

Takeda concur with the Delegate's recommendation that Adcetris has a positive benefit risk balance for use in patients with relapsed or refractory CD30+ HL post ASCT or after failure of at least 2 prior therapies where ASCT or multi-agent chemotherapy is not a treatment option and patients with relapsed or refractory sALCL. Takeda acknowledge that the recommendation for use in the subset of patients who had not received prior ASCT is less robust, however it is equally true that for patients whose lymphoma was refractory to salvage therapy and for whom ASCT was not an option, the prospect of long-term survival is bleak and therefore this represents an even higher-risk patient group, with additional unmet clinical need.

Benefit/risk in specific patient populations

In addition to the 20-patient population described in the main dossier, EMA's assessment included additional data provided at their request for HL patients with no prior transplant who received three weekly 1.8 mg/kg brentuximab vedotin. These best overall response and safety data were provided to TGA. This report describes 59 patients who received any brentuximab vedotin dose and schedule, as well as the subpopulation of 41 patients who received the SmPC-recommended 1.8 mg/kg brentuximab vedotin dose every 3 weeks (three weekly). This 41-patient set included 26 patients from the sponsor's Named Patient Program and a further 15 patients from clinical studies as follows: 2 patients from Study SG035-0001, no patients from weekly dosing Study SG035-0002, efficacy data for 7 patients in the corrected Q-T interval (QTc) Study SGN35-007 not reported in the main dossier, and preliminary data for 6 patients enrolled in Japan-only Study TB-BC010088.

With a 54% overall response rate in this 41-patient dataset, a CR rate of 22%, and the ability to permit subsequent autologous or allogeneic stem cell transplant in 19% of these patients who had previously been unable to receive a stem cell transplant, brentuximab vedotin has thus far shown meaningful efficacy in this patient population with limited options and a very poor prognosis.

Use in hepatic impairment

Takeda disagree with the Delegate's proposed amendments to the PI with regards to the use of Adcetris in patients with hepatic impairment.

The reduction in the recommended starting dose for patients with hepatic impairment was based on data from recently completed Study SGN35-008 Part B, exploring a dose of 1.2 mg/kg three weekly in patients with hepatic or renal impairment. This reduced starting dose is currently under review by both the US FDA and EMA. Adcetris was already available in each region with no recommended dosage adjustment for patients with

[20] Brentuximab vedotin Periodic Safety Update Report (PSUR) covering the period from 19 Feb 2013 to 18 Aug 2013. Dated 10 Oct 2013.

hepatic impairment, thus revisions to the respective prescribing information documents were submitted at the earliest opportunity once these new data became available.

Takeda concur with the Delegate's assessment that available PK data suggest a less favourable benefit-risk ratio in patients with hepatic impairment, that available safety data are confounded by comorbidities, and that data to date show variations in MMAE concentrations across degrees of hepatic impairment. Nonetheless, the severity of relapsed or persistent HL and sALCL, the lack of effective treatment options for these patients, and objective responses reported for doses as low as 0.6 mg/kg three weekly in patients without organ impairment in Phase 1 Study SG035-0001 all suggest that a reduced starting dose of 1.2 mg/kg brentuximab vedotin should be an option available to treating physicians for patients with relapsed or refractory HL or sALCL and hepatic impairment.

The relapsed/refractory HL and sALCL patient populations for which Adcetris is intended currently have no effective alternative treatment options; as such, the clinical implications of implementing a broad recommendation to contraindicate use in patients with any degree of hepatic impairment need consideration, as do the potential implications for patients who may develop hepatic impairment during treatment and become in eligible for potentially life-saving treatment.

Takeda propose that Adcetris at a dose of 1.2 mg/kg remains a clinically relevant treatment option for patients with impaired hepatic function. To support this, Takeda have revised the proposed PI text, in particular the Precautions – Use in Hepatic Impairment section, seeking to explicitly advise the treating physician that the data are limited and that Adcetris must be used with caution in patients with hepatic impairment. The proposed text further specifies that such patients should be closely monitored for adverse events, and that Adcetris treatment should be discontinued in those patients with hepatic impairment whose disease does not demonstrate adequate response to treatment.

Peripheral neuropathy

Takeda concur with the Delegate's description of the peripheral neuropathy (PN) associated with brentuximab vedotin. Of the patients in the pivotal studies, 56% experienced any grade of PN, whereas Grade 3 events were experienced by 13% of patients and no Grade 4 events were reported. PN events were typically reversible, with a 16-week median time from onset to resolution. In the Phase II population, at the time of last evaluation, the majority of patients experiencing PN (62%) had improvement or resolution of their PN symptoms.

Pancreatitis

With respect to the Delegate's comment regarding Pancreatitis, Takeda wish to clarify that a Precaution for pancreatitis was proposed for inclusion into the PI on 14 October 2013. This proposal was based on a Company Core Safety Information update resulting from a cumulative review of available data for events of acute pancreatitis.

A review of acute pancreatitis cases in the Global Safety Database has identified 12 reports including 6 with a possible causal association with Adcetris treatment (3 clinical trial reports and 3 post marketing reports). The estimated incidence of acute pancreatitis derived from clinical trial data is uncommon (0.27%) and the post marketing reporting rate (with its data limitations) is rare (0.07%).

In conclusion, Takeda consider acute pancreatitis a new and important potential risk associated with Adcetris therapy, and have therefore proposed amendments to the PI and RMP. In the absence of placebo- or comparator-controlled data or epidemiological data that provide background incidence rates in the relapsed and refractory lymphoma population, an absolute causal association between Adcetris treatment and pancreatitis cannot be established at this time. This new and important potential risk of acute

pancreatitis does not alter the overall favourable benefit-risk balance of Adcetris treatment in patients with relapsed/refractory HL or sALCL.

Other matters

Duration of therapy

With reference to the Delegate's comment regarding the removal of the 16 cycle cap from the US PI, please be advised that this application was based on new data not included in the Australian dossier. A cross-study report detailing safety data for 19 patients previously enrolled in other brentuximab vedotin studies who were next enrolled in extended therapy or retreatment Study SGN35-006 and ultimately received greater than 16 cycles of treatment was submitted to the US FDA. These safety data, although in a limited sample, suggest a safety profile similar to that reported in the dossier population and supported the change to the US PI.

At this time Takeda do not intend to seek a similar revision to the Australian PI for Adcetris.

Quality data evaluation

Please be informed that all outstanding Quality items have been completed. Takeda believe that there are no further objections to the registration of Adcetris.

The updated EU RMP (v3.0) and Australian specific Annex (v3.0) are provided to TGA. Updates to the potential risks have been included as requested by the RMP evaluator.

Conclusion

Takeda concur with the Delegate's proposed action to approve Adcetris (brentuximab vedotin) 50 mg Powder for Injection for the:

> Treatment of adult patients with relapsed or refractory CD30+ Hodgkin Lymphoma (HL):
>
> - Following autologous stem cell transplant (ASCT) or
> - Following at least two prior therapies where ASCT or multi-agent chemotherapy is not a treatment option.
>
> Treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma.

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 submission seeks to register a new chemical entity.

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Adcetris powder for injection containing 50 mg of brentuximab vedotin to have an overall positive benefit–risk profile for the Delegate's amended indication**;**

> *Treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL):*
>
> - *Following autologous stem cell transplant (ASCT) or*
> - *Following at least two prior therapies where ASCT or multi-agent chemotherapy is not a treatment option.*

Treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL).

Specific advice:

The ACPM also provided the following specifically requested advice:

Is evidence from Phase II, uncontrolled studies sufficient to proceed with registration?

The ACPM was of the view that the very favourable benefit-risk ratio of brentuximab monotherapy in Phase II trials for the proposed indications was adequate evidence. There are no Phase III studies but HL is an uncommon disease, sALCL is very rare and candidates for brentuximab vedotin represent but a small subset of these groups. In addition, there is no established standard of care for Phase III comparison. The primary endpoint of overall response rate (ORR) was not ideal but progression free survival (PFS) and overall survival (OS) were also reported and assessment of response rate permitted comparison with response to previous treatment in the same patient, which provided useful supportive evidence of efficacy.

In what patient population(s) does the ACPM see a positive benefit–risk balance for use o*f Adcetris?*

The data show greater benefit-risk for patients post high dose chemotherapy (HDC)/ASCT than for those having several previous chemotherapy regimens but no HDC/ASCT. However, durable complete responses were seen in both groups. More data on the impact of peripheral neuropathy on quality of life would be valuable.

Should use be recommended in patients with hepatic impairment?

- The liver is a major route of elimination and in hepatic impairment exposure to MMAE may 2.3 fold, with reduced ADC exposure.
- Given the limited data in patients with hepatic impairment the recommended dosing reduction to 1.2 mg/kg and close monitoring for toxicity is prudent and reasonable.
- Should patients with hepatic impairment develop significant neuropathy this would likely occur relatively late in treatment and be reversible, that is provide sufficient time to assess the benefit: risk ratio of ongoing therapy.
- While a higher monomethyl auristatin E (MMAE) AUC may result in increased neutropenia, conversely it is arguable that the reduced Adcetris exposure may reduce the risk of neutropenia.
- The projected benefit: risk ratio in all patients justifies cautious use of brentuximab in patients with hepatic impairment rather than exclusion. The current SGN35 008 Part B study will provide further data and ongoing approval should be contingent on confirmation of efficacy and safety

In making this recommendation the ACPM:

- Noted it is moot whether CD30 positivity needs to be stipulated for HL.
- Noted the pharmacology appears well established. The sponsors' argument about capping doses for patients, particularly women, over 100 kg is not particularly well supported, especially given the increasing body of evidence in favour of using actual body weight in cytotoxic dosing.
- Expressed concern that Adcetris is to be marketed in a single 50 mg vial
  - The dosage recommendation is 1.8 mg/kg IV infusion every three weeks.

- For an average 60 kg female dosing of 1.8 mg/kg equals a dose of 108 mg will require three 50 mg vials with a discard of 42 mg (84%) of the third vial.
- To avoid either drug wastage, or risk of compromising either safety (from dose increases) or efficacy (from dose reductions) due to any dose rounding that may occur Adcetris should also provided in 10 mg vials

Proposed conditions of registration:

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

- Subject to satisfactory implementation of the Risk Management Plan most recently negotiated by the TGA,
- Negotiation of Product Information and Consumer Medicines Information to the satisfaction of the TGA.
- Submission of the report from the on-going Study SGN35 008 Part B when available.

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

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following:

- A statement in the *Precautions* section of the PI and relevant sections of the CMI that there is insufficient evidence to judge the safety of treatment extended past 12 months.

The ACPM advised that the 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 Adcetris powder for injection vial containing brentuximab vedotin rch 50 mg for intravenous infusion indicated for:

Treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL):

- *Following autologous stem cell transplant (ASCT) or*
- *Following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option*

Treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL).

Specific conditions of registration applying to these goods

The Adcetris EU Risk Management Plan (EU-RMP) Version 2.0 (dated 17 April 2013, DLP 18 February 2013) and Australian-Specific Annex version 2.0 (dated July 2013) included with submission PM-2012-03441-I-4, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The Product Information approved for main TRADENAME at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>. The PI for OTHER TRADENAMES is identical except for the product name.

Attachment 2. Extract from the Clinical Evaluation Report

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