Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for brentuximab vedotin

Proprietary Product Name: Adcetris

Sponsor: Takeda Pharmaceuticals Australia Pty Ltd

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TGA Health Safety Regulation

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About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

List of abbreviations

Abbreviation	Meaning
ADC	Antibody drug coagulate
ALCL	Anaplastic large cell lymphoma
ASCT	Autologous stem cell transplant
ATA	Anti-tumour antibody
DDI	Drug to drug interaction
GMR	Geometric mean ratio
IRF	Independent review facility
MMAE	Monomethyl auristatin E
SAE	Serious adverse event
TEAE	Treatment emergent adverse event

1. Introduction

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

- the chimeric 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.

The proposed dosage of Adcetris is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every three weeks.

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.

3. Contents of the clinical dossier

3.1. Scope 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 QT-corrected, QT interval study, Study 007 an
- 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.

3.2. Paediatric data

This submission did not include paediatric data.

3.3. Good clinical practice

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

4. Pharmacokinetics

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 CYPs 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.

4.1. Summarising the results of the individual studies

Study 0001 was a Phase I first in human single-arm open label multicentre dose escalation study of Adcetris administered IV every three weeks as a single agent in patients with relapsed/refractory CD30+ haematological malignancies. The primary objectives were to assess safety and tolerability and determine MTD. The secondary objective was to assess the PK, the incidence of anti-tumour antibodies and anti-tumour response. The starting dose of Adcetris for the trial was 0.1 mg/kg for patients in the first cohort and the study employed a standard 3 plus 3 design. PK evaluation included individual patient blood concentrations and parameters for Adcetris and MMAE. Multiple samples were taken for PK analyses through all cycles of treatment.

A total of 45 patients were enrolled in the study and received at least one dose of Adcetris. Three patients received 0.1 mg/kg, four 0.2 mg/kg, three 0.4 mg/kg, three 0.6 mg/kg, three 0.8 mg/kg, four 1.2 mg/kg, 12 1.8 mg.kg, 12 2.7 mg/kg and one patient 3.6 mg/kg. Median age of the patients were 36 years with four patients being > 65 years. Sixty-two percent of the patients were men and 87% white. Diagnoses were HL for 42 patients, ALCL for two patients and angioimmunoblastic T-cell lymphoma for one patient.

Results revealed that increases in brentuximab vedotin ADC exposure were approximately dose proportional. First dose geometric mean terminal half-life was between 4-6 days for the 1.8 and 2.7 mg/kg dose. Median time to maximum plasma concentration (T_{max}) typically occurred immediately after the end of the infusion. Steady state for brentuximab vedotin ADC was achieved by cycle 2 consistent with a T½ estimate. No accumulation was detected at the 1.8 mg/kg dose and accumulation was slight at the 2.7 mg/kg dose. Geometric mean ratios for the $AUC_{0\text{-}21\ days}$ between cycles ranged from 0.93 – 1.24 and the observed C_{max} geometric mean ratio ranged from 0.73 to 1.11.

Increases in MMAE were approximately dose proportional. First dose apparent $t_{1/2}$ was between 3-4 days for the 1.8 and 2.7 mg/kg doses and median T_{max} occurred approximately two days post-dose for the 1.8 mg/kg dose and approximately three days post-dose for the 2.7 mg/kg dose. Steady state MMAE was achieved by cycle 2. MMAE AUC_{0-21} days and C_{max} decreased following multiple doses.

Total antibody exposures were higher than for brentuximab vedotin and ADC exposures while T_{max} was similar. Anti-tumour antibodies (ATAs) were confirmed in two patients, the PK of brentuximab vedotin did not appear to be meaningfully affected.

Study 0002 was a Phase I single-arm open label multicentre dose escalation study of Adcetris administered IV weekly for three weeks of every four week cycle as a single agent or in combination with Gemcitabine in patients with relapsed/refractory CD30+ haematological malignancies. The primary objectives were to assess safety and tolerability and determine MTD. Secondary objectives were to assess PK, the incidence of ATA and anti-tumour response. Study treatment included brentuximab vedotin at a study dose of 0.4 mg/kg in the first cohort employing a standard 3 plus 3 design. Patients could remain on treatment for up to 12 cycles or until disease progression whichever occurred earlier. PK parameters were derived from blood concentration versus time data.

Reviewing results, 44 patients received at least one dose of brentuximab vedotin in the study. No patients received Gemcitabine. Four patients received 0.4 mg/kg dose, four 0.6 mg/kg, six 0.8 mg/kg, 12 1 mg/kg, 12 1.2 mg/kg and six 1.4 mg/kg. The median age of patients was 33 years with a range of 12-82 years, two patients were older than 65 years. Seventy percent were men and 84% were white. Diagnosis for HL for 38 patients, ALCL for five patients and peripheral T-cell lymphoma for one patient.

Across the doses tested increases in brentuximab vedotin ADC exposure were approximately dose proportional. The median first dose T_{max} occurred between 0.03 and 0.09 days after the start of infusion. For ADC the $AUC_{0-7\ days}$ ranged from 0.67 to 1.75 across all cohorts. The corresponding range for C_{max} was from approximately 0.92 to 1.76 across all cohorts.

Increases in MMAE exposure were approximately dose proportional. The median T_{max} occurred between 1.03 and 3.03 days after the start of infusion. Generally MMAE $AUC_{0-7\ days}$ and C_{max} did not decrease following multiple doses. The observed GMR ranged from 0.89 to 1.29 in the observed C_{max} GMR.

Total antibody exposure status, that is $AUC_{0-7\ days}$ and to a lesser extent C_{max} were higher in brentuximab vedotin ADC exposure while T_{max} was similar. The accumulation of ADC and MMAE was moderate. The intra and inter-cycle accumulation ratio for ADC was approximately 1.72 at 1 mg/kg and 1.28 and 1.2 mg/kg.

Five patients or 11% had ATA at cycle 1 day 1 visit and 14 patients or 33% had ATA at the post-baseline visit.

Study 008A was a Phase I three-arm open label multicentre DDI and excretion study of brentuximab vedotin (1.2 mg/kg or 1.8 mg/kg) IV every three weeks in patients with CD30+ haematological malignancies. The primary objects were to assess the effect of brentuximab vedotin on the PK of a CYP3A4 substrate (Midazolam) to assess the effect of CYP3A4 inducer (Rifampin) on the PK of brentuximab vedotin and to assess the effect of CYP3A4 inhibitor (Ketoconazole) on the PK of brentuximab vedotin and to determine the primary route of excretion of MMAE. Secondary objectives were to assess safety and tolerability, to assess the incidence of ATA and to identify the excretion metabolites of MMAE. Patients received brentuximab vedotin 1.8 mg/kg or 1.2 mg/kg by IV infusion on day 1 or each three week cycle.

Fifty-six patients enrolled in the study and received study drug. Sixteen patients in Arm A-mid, 21 patients in arm A-rif and 19 patients Arm A-ket. Forty-five patients were evaluable for PK: 15 patients in Arm A-mid, 14 patients in Arm A-rif and 16 patients in Arm A-ket. Eight patients were evaluable for excretion analysis.

The median age of the 45 patients in the PK analysis set was 38 years with a range of 16-71 years; 64% of patients were men and 84% were white. Forty patients or 89% had HL, three patients or 5% has systemic ALCL and two patients or 4% had other cancer diagnoses.

In reference to PK parameters $AUC_{0\text{-infinity}}$ and C_{max} for Midazolam between Midazolam alone compared with Midazolam co-administered with brentuximab vedotin, the 90% CI for $AUC_{0\text{-infinity}}$ was within bioequivalence bounds (0.80, 1.25) showing that brentuximab vedotin MMAE do not affect the $AUC_{0\text{-infinity}}$ of Midazolam when Midazolam is administered at the maximum concentration of MMAE approximately two days after brentuximab vedotin administration. This result supports the conclusion that brentuximab vedotin is neither an inhibitor nor inducer of CYP3A4.

The effect of Rifampin a CYP3A4 and P-gp inducer on the PK of brentuximab vedotin was determined by the same parameters as that used for Midazolam. For the ADC 90% the CI for both $AUC_{0\text{-infinity}}$ and C_{max} were within bioequivalence bounds indicating that a CYP3A4 inducer had no effect on the ADC and that ADC exposures were consistent between cycles 1 and 2.

Results showed that the MMAE exposures are lower when brentuximab vedotin is co-administered with a daily dose of Rifampin with the upper 90% CI bound for $AUC_{0\text{-infinity}}$, $AUC_{0\text{-10 days}}$ and C_{max} being < 1. MMAE is likely a substrate of CYP3A4 and/or P-gp.

The effect of Ketoconazole, a strong CYP3A4 and P-gp inhibitor on the PK of brentuximab vedotin, was also compared utilising the same PK analyses. Again these data effectively showed that a strong CYP3A4 inhibitor had no effect on the ADC and that ADC exposure was consistent between cycles 1 and 2.

For MMAE the results suggest that the MMAE exposure is higher when brentuximab vedotin is co-administered with Ketoconazole with the upper 90% CI bound for the PK parameters being more than 1. The results also suggest that MMAE is likely a substrate of CYP3A4 and/or P-gp.

In relation to excretion, eight patients were evaluable for excretion analyses and approximately 23.5% of the MMAE received during a brentuximab vedotin infusion was recovered in both urine and faeces over a one week period. Of the MMAE recovered the median percentage of MMAE excreted in faeces was 72% with a range of 59-77% with the remainder excreted in urine.

Study 007 was a Phase I single-arm open label multicentre cardiac ventricular repolarisation study of brentuximab vedotin 1.8 mg/kg IV q 3 weekly in patients with CD30+ haematological malignancies. The primary objective was to evaluate the effect of brentuximab vedotin on cardiac ventricular repolarisation. Additional objectives were to evaluate other ECG parameters, investigate the relationship between corrected QT (QTc) interval and MMAE concentration; investigate the relationship between QTc interval and proarrhythmic events and assess safety. A pre-defined primary analysis was the change from baseline to multiple time points in cycle 1 in the duration of ventricular repolarisation using QTcF. Intensive ECG monitoring was conducted during the first four days of cycles 1 and 3. Blood samples for investigation of QTc intervals/MMAE concentration relationships were obtained at each ECG monitoring period.

Fifty-two patients were enrolled in the study and received at least one dose of brentuximab vedotin. Patients had a median age of 35 years with a range of 19-76 years and three patients were > 65 years. Forty-eight percent of patients were men and 52% were women. Diagnosis of HL for 49 patients, systemic ALCL for two patients and CDC+ Grade I lymphoma for one patient. Forty-six patients were included in the evaluable patient set.

The study met its primary endpoint by demonstrating that the upper bound of each 90% CI had a mean effect on QTcF was < 10 msecs at each time point. These data indicated that brentuximab vedotin did not meaningfully prolong the QTc interval when administered at a dose of 1.8 mg/kg brentuximab vedotin was not associated with the appearance or worsening of clinically notable proarrhythmic adverse events or the appearance or worsening of morphologic abnormalities of interest.

In cycle 1 the estimated C_{max} for MMAE was 7ng/ml which is consistent with MMAE exposures expected following administration of a single dose of 1.8 mg/kg. No significant relationship was observed between plasma MMAE concentrations and the change in QTcF from baseline to days 1, 2, 3 or 4.

4.2. Evaluator's discussion

These data therefore indicate that it is not expected to be a clinically significant effect of Adcetris on cardiac repolarisation.

Review of PK parameters of brentuximab vedotin in relation to ADC, MMAE and TAb and the metabolism of MMAE in humans was evaluated from Studies 0001 and 008 as these studies involved the 1.8 mg/kg at every three week dosing schedule.

The PK of ADC after an IV dose was similar to that for other antibody products. Maximum concentrations were typically observed at the end of the infusion or sampling time closest to the end of infusion. A multi-exponential decline in ADC serum concentrations were observed with a t1/2 of approximately 4-6 days. The PK of ADC were linear exposure dose proportional with 0.1- 2.7 mg/kg. It is noted that steady state was observed by 21 days consistent with t1/2 estimates. Minimal to no accumulation was observed in multiple doses of the Q3 week regimen and the ADC exposure did not decrease with subsequent doses.

MMAE appeared to follow metabolite kinetics with the elimination of MMAE appearing to be limited by its rate of release from ADC. T_{max} ranged from approximately 1-3 days. MMAE PK was approximately linear with exposure increasing approximately dose proportionally. After multiple doses of brentuximab vedotin every three weeks MMAE steady state was achieved by 21 days similar to that for ADC. MMAE exposures decreased after multiple doses with approximately 50-80% of the exposure of the first dose being observed at subsequent doses.

The serum PK of TAb following an IV dose of brentuximab vedotin involved maximum concentrations which were typically observed at the end of infusion. Exposures were approximately dose proportional and higher than those associated with ADC. The proportion of TAb to ADC increased with time suggesting that the t1/2 of the unconjugated antibody was longer than that of ADC.

A population PK approach was undertaken to assess the effects of gender, age, race, body weight, body surface area and disease either HL or ALCL on the PK of brentuximab vedotin and MMAE. The intrinsic factors were determined to be statistically significant with gender for ADC, titre by cycle for ADC, manufacturing process B for MMAE, baseline albumin for MMAE and weight/body surface area for both ADC and MMAE. Weight was the only clinically meaningful co-variate. Accordingly it is considered appropriate to cap the dose of brentuximab vedotin for patients who are > 100kg weight.

Review of renal function in relation to population PK analysis revealed that the majority, that is 89% of patients had normal renal function. In an exploratory analysis of patients with low calculated creatinine clearance ADC clearance appeared to be affected by severe renal impairment while MMAE apparent clearance appeared to be affected by moderate and severe renal impairment. Accordingly it is noted that brentuximab vedotin should be administered with caution in patients with estimated creatinine clearance of < 30ml/min.

An exploratory analysis of population PK by hepatic function revealed that there was no clear correlation between the collective indicators of hepatic function and the effects on MMAE and ADC PK.

Review of the development of ATA according to population PK analyses revealed the majority of patients, that is 95% in the Phase II study population tested negative for ATA at baseline. Most patients, that is 61% remained ATA negative although 27% became transiently positive and 7% became permanently positive after exposure to brentuximab vedotin. The majority of these who

became positive had this occur at the beginning of cycle 2. There was no evidence that ATA positivity had any effect on PK parameters.

4.3. Evaluators summary

These PK data have therefore shown a quite comprehensive determination of a PK for Adcetris. No untoward relationships were determined from these analyses.

5. Pharmacodynamics

None.

6. 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.

7. Clinical efficacy

7.1. Phase I studies

Two Phase I studies presented in this evaluation namely 0001 and 0002 provided data with relevance to efficacy. Study 0001 involved administration of Adcetris on a three weekly schedule as a single agent. The pre-treatment characteristics for this study were presented in the PK section. Planned enrolment for the study was up to 51 patients and all patients required measurable disease. Patients with Hodgkin's lymphoma had disease that had failed systemic chemotherapy induction or salvage and were ineligible for, refused treatment by or previously had had an ASCT. Patients with sALCL were either beyond first remission or had disease that was refractory to frontline chemotherapy. During all phases of the study if an objective response was observed then patients were eligible to receive two additional cycles of treatment at that dose level. As previously indicated in Study 0001 the defined starting dose was 0.1 mg/kg with progressive dose escalation to 3.6 mg/kg. As MTD was determined at a dose of 1.8 mg/kg a total of 12 patients were treated at this dose level.

Also a total of 10 patients who received 2.7 mg/kg were treated at that dose level.

Disease evaluation was by CT or CT/PET scans as well as clinical evaluation. Tumour responses were assessed after every two cycles of treatment.

A total of 45 patients were enrolled in the study. The diagnosis was HL for 42 patients, sALCL for two patients (one patient in the 1.2 mg/kg cohort and one in the 2.7 mg/kg cohort) and angioimmunoblastic T-cell lymphoma for one patient in the 0.2 mg/kg cohort. All patients had received prior systemic chemotherapy with a median of three regimens and a range of 1-7.

Other previous treatments were ASCT in 33 patients, radiotherapy in 27 patients and cancer related surgery in 14 patients.

In the efficacy evaluable set of 42 patients, objective responses were achieved in 40% including CR for 11 patients or 26%, PR for six or 14%, SD for 17 or 40% and PD for eight. Objective responses generally occurred at the high dose levels, that is > 1.2 mg/kg although two patients with 0.6 mg/kg achieved a PR. The overall response rate at the MTD of 1.8 mg/kg was 50%. Overall 30% of patients with HL achieved response and of the two patients with sALCL both had a best clinical response of CR.

Of the 17 patients with an objective response, eight or 47% had disease progression or death at time of study closure. The estimated median duration of response by Kaplan-Meier analysis was 75.4 weeks with a range of 2.7 to 84.6+ weeks with over half of the patients with objective response, that is 11/17 having a response duration of at least six months. The estimated median progression free survival was 27 weeks with a range of 3-96 weeks and the estimated median survival was 102 weeks with a range of 2-126.1 weeks.

The second Phase I Study 0002 again a single-arm open label multicentre dose escalation study utilised 0.4-1.4 mg/kg IV as a weekly schedule every three weeks for a four week cycle. Pre-treatment characteristics have again been outlined in the PK section. Planned enrolment was approximately 39 patients with an allowance up to a maximum of 72 patients to accommodate dose escalation and expansion cohort. All patients had histologically confirmed CD30+ haematological malignancy and measureable disease of at least 1.5cm by radiographic technique. HL patients had failed systemic chemotherapy and were ineligible for, or refused treatment by or previously had ASCT. Patients with sALCL were beyond first remission or refractory to frontline chemotherapy. Patients with clinical benefits were eligible to receive up to six cycles. Disease evaluation was comparable to Study 0001.

A total of 44 patients enrolled in the study had all received at least one dose of brentuximab vedotin. The diagnosis was HL for 38 patients, systemic ALCL for five patients and peripheral T-cell lymphoma for one patient. All patients had received prior systemic chemotherapy with a median of three regimens range 1-8. Other previous treatments included ASCT in 30 patients, radiotherapy in 27 patients and cancer related surgery in seven patients. Of the 38 patients with HL, 10 patients had not received ASCT.

Of the 38 patients diagnosed with HL objective responses were observed in 20 patients or 53% and best overall response was CR for 10 patients or 26%, PR for 10 patients or 26%, SD for 12 patients or 32% and PD for four patients or 11%. Of the five patients with sALCL four had best clinical responses of CR, two with 0.8 mg/kg and two with 1.1 mg/kg and one had a best response of stable disease at 0.4 mg/kg.

Of the 24 patients with objective response, nine had disease progression or death at time of study closure, the estimated median progression free survival using Kaplan-Meier analysis was 28.7 weeks with a range of 7.3 – 83.6+ weeks. The low rate of patients who died during study prevented assessment of overall survival.

7.2. Evaluator's discussion

These data show that there was clear cut evidence of significant clinical response in the two studies which were essentially comparable to one another. It is noted that adverse effects were clearly greater in the weekly schedule of therapy and accordingly the three weekly schedule was determined to be the most appropriate for evaluation in further studies.

7.2.1. Hodgkin's lymphoma

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.

Study treatment was administered as a 30 minute out-patient infusion on the first day of each three week treatment period. Maximum duration of treatment was 16 cycles or approximately one year. Dose delays were up to three weeks and reductions to 1.2 mg/kg were allowed for toxicity. After completing treatment or upon treatment discontinuation due to disease progression or unacceptable toxicity patients entered long term follow up for disease status and survival determination.

The primary endpoint of the study was overall response rate based on independent review facility assessment. Response assessments were made according to the revised response criteria for malignant lymphoma. Treatment responses were assessed by spiral CT of chest, neck and abdomen and pelvis, from PET scans and clinical data. Secondary efficacy endpoints were duration of objective response, complete response rate, progression free survival as per independent review facility and overall survival. Also assessed were B symptom resolution rate, measure of clinical benefit and event free survival. Principal cut-off date for patient's assessment was 20th December 2010 which extended to the date of the last patient's end of treatment visit and at least three days after final dose of Adcetris. An additional 12 months follow up to assess secondary efficacy endpoints including duration of objective response, progression free survival, overall survival with a data cut off point of the 1 August 2011.

One hundred and two patients were enrolled on the study and the baseline disease characteristics and prior therapy. The study population was generally balanced with regard to gender and was primarily white. The median age was 31 years and three patients were at least 65 years of age and one patient was younger than 18 years. Patients entered into the study were generally ambulatory and able to perform normal activities without assistance with an ECOG performance status of zero or 1. Approximately half of the patients, that is 46% had stage II disease at initial diagnosis, 26% stage III and 20% stage IV while 4% had stage I and 4% unknown disease. Relative to most recent therapy 58% of patients were relapsed and 42% were refractory. Notably 71% of patients had primary refractory disease defined as not achieving a best response of CR with frontline therapy or < 3 months had elapsed since the date of the last dose of frontline therapy to the date of progression. Nine patients were identified as never having responded to any prior cancer related systemic therapy. All patients had previously received ASCT with 89% of patients with one transplant and 11% two transplants and all had received at least one prior regimen of systemic chemotherapy with a median of 3.5. The median time from ASCT to relapse was 6.7 months and 71% of patients experienced relapse within one year of ASCT.

It is noted that all patients who had previously received allogeneic SCT were excluded from all three studies. Also excluded were patients with congestive heart failure, history of another primary malignancy within three years, known cerebral/meningeal disease, current therapy with other antineoplastic agents, inability to give informed consent and known hypersensitivity to any excipient in the drug formulation.

In relation to patient disposition the most common reason for treatment discontinuation being disease progression or relapse followed by adverse event. The most common reasons for status discontinuation, that is discontinuation of post-treatment follow up, was patient death. Study drug exposure had a longest median duration of treatment for the pivotal study, that being 27 weeks with a range of 3-56 weeks and a median total dose of 1184 mg with a range of 150-2880.

Considering the results in the intent to treat analysis set of 102 patients, the overall response rate per IRF was 75% with 95% CI being 64.9, 82.6%. Thirty-four patients achieved complete response or 33% and 42 patients achieved partial remission or 41%. These response rates were determined by the IRF after review of investigator assessments. Tumour size reductions from baseline were observed in 94% of all patients.

At the time of the data cut off, 61 patients or 50% remained in active follow up. The median duration of objective response per IRF by Kaplan-Meier analysis was 6.7 months with 95% CI being 3.6, 14.8 months with a range of 1.2+ - 26.1+ months. The median duration of response had not been reached in patients with a best overall response of CR with a range of 1.4 – 26.1+ months.

Reviewing secondary endpoints, the estimated median progression free survival for patients in the ITT set analysed by Kaplan-Meier methods was 5.6 months with 95% CI being 5-9 months and a range of 1.2-27.3+ months. The estimated progression free survival rate at three months was 81% and at six months 47% and at 12 months 34% and at 24 months 23%.

The estimated mean duration of overall survival was 27 months with a range of 1.8-27.3 months with 36 deaths among the 41 patients no longer on active follow up at the time of data cut off. The estimated overall survival rate of three months was 99% and 12 months 89% and at 24 months 61%.

Median event free survival is 29 weeks with 95% CI being 23.9 – 38.3 weeks by Kaplan-Meier analysis for the ITT set. The B symptom resolution rate was 77%, that is 27/35 patients with B symptoms at baseline and a median time to resolution of B symptoms was 3.1 weeks with a range of 0.4-11.9 weeks.

In order to further assess response rates, analysis was undertaken to compare Adcetris and progression free survival achieved compared to progression free survival achieved with the most recent systemic therapy after ASCT. This illustrates advantage for Adcetris.

In addition an assessment of progression free survival achieved with Adcetris versus progression free survival achieved with most recent prior systemic therapy included patients for whom ASCT was the most recent therapy. This is again demonstrating benefit for Adcetris.

An intra-patient comparison of progression free survival for last chemotherapy received prior to study entry with progression free survival for Adcetris per investigator again demonstrates benefit across the range of patients.

Event free survival data indicating 81 patients or 79% had disease progression or discontinued treatment with a median event free survival by Kaplan-Meier analysis of 29 weeks and event free survival rate at 12 months being 20%.

Intra-patient comparison of time to tumour progression with Adcetris versus time to tumour progression with the most recent post-ASCT systemic therapy demonstrates benefit for Adcetris.

Review of the overall response rate for patients with primary or refractory disease revealed that this is slightly lower than for those patients who did not have primary or refractory disease with 51/72 patients achieving response or 71% versus 25 or 30 patients or 83%. The CR rate however was similar at 35% for patients with primary or refractory disease versus 33% for those who did not have primary or refractory disease. It is also noteworthy that of the nine patients refractory to all prior therapy five achieved a best response for CR and two achieved a best response for PR.

Overall response rate according to individual pre-treatment factors all demonstrated significant efficacy for Adcetris although the only slight deviation was in a small number of patients with bone marrow involvement present.

7.2.1.1. Evaluators comments

These 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.

7.2.2. Systemic anaplastic large cell lymphoma (sALCL)

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.

Study treatment was administered as a 30 minute outpatient IV infusion on the first day of each three week treatment period. Maximum duration of treatment was 16 cycles. Dose delays of up to three weeks and reductions to 1.2 mg/kg were allowed for toxicities. Study treatment was discontinued upon disease progression or unacceptable toxicity.

The primary endpoint was overall response rate based on IRF assessment of best clinical response. Treatment responses were assessed by spiral CT, PET scan and clinical review at intervals. Secondary efficacy endpoints were duration of objective response, complete response rate, progression free survival and overall survival. Also assessed were event free survival and B-symptom resolution rate.

Patient enrolment was 58 patients. Fifty-seven percent of the patients were male with a median age for all patients of 52 years and nine patients > 65 years.

In relation to disease characteristics and prior treatment the highest percentage of patients had stage IV disease, that is 36% followed by stage II at 22% and stage I at 19% and stage III at 14%. Both ALK+ and ALK- patients were enrolled with 16 being ALK+ and 42 being ALK- . Patients had received a median of two prior systemic chemotherapy regimens with a range of 1-6 and 15 patients or 26% had received a prior ASCT and 26 patients had received prior radiotherapy. Thirty-six patients or 62% were classified as primary or refractory disease having not achieved a best response of CR with frontline therapy or < 3 months elapsed since the date of their last dose of frontline therapy to date of progression and 13 patients or 22% had never responded to any previous therapy.

Exclusion criteria were similar to those for a Study 0003.

In relation to patient disposition, the most common reason for treatment discontinuation was adverse event in 16 patients followed by investigator decision in 14 patients and progressive disease in 13 patients.

In the ITT analysis set of 58 patients, the overall response rate per IRF was 86% with a 95% CI of 74.6, 93.9 and a 59% complete response rate (34 patients) and a 28% partial response rate.

The percentage of patients with tumour reduction was calculated for the ITT set in the study.

In relation to duration of response 27/50 patients had disease progression by IRF assessment or had died by the time of analysis. Median duration of objective response by Kaplan-Meier analysis was 13.2 months and 95% CI 5.7 and range 0.1-21.7+ months. For those patients who achieved complete remission the median duration of response had not been reached.

In relation to progression free survival by IRF Kaplan-Meier analysis this was 14.3 months with a lower bound of 0.69 months with a range of 0.8-23.6 months. The estimated rate of PFS at three months was 81%, six months 65%, nine months 58%, 12 months 54% and 24 months 37%.

At the time of the data cut-off for the final review, 19 patients had died and median overall survival had not been reached. The estimated survival rate at three months was 93% and six months 83%, 12 months 70%.

In relation to other efficacy endpoints the B-symptom resolution rate was 82% or 14/17 patients with B-symptom at baseline with a median time to resolution of 3.14 weeks.

Median event free survival was 6.7 months for patients in the ITT set.

A comparison of median progression free survival for patients receiving Adcetris per investigator assessment compared to most recent prior therapy delivered either with or without ASCT indicates Adcetris progression free survival of 14.5 months versus most recent prior therapy at 5.9 months.

In relation to time to tumour progression the median time to tumour progression with Adcetris was 20 months compared to last prior therapy at 5.9 months.

Malignant cutaneous lesions were present in 15 of these patients and complete resolution with Adcetris occurred in 14 or 93% of these.

In relation to response, for those patients with primary refractory disease this was 76% or 22/29 patients compared to those with relapsed disease who had response in 28/29 patients or 97%. The CR rate for relapsed disease was 69% compared with refractory disease at 48%.

Thirteen patients had never achieved an objective response with any prior therapy and the overall response rate for these patients was 77% or 10/13 patients with a CR rate of 38%.

7.2.2.1. Evaluators comments

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.

8. Clinical safety

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. Data on these studies has been earlier discussed in relation to pharmacology and efficacy. Across the six completed clinical studies summarised in this submission a total of 357 patients received at least one dose of Adcetris. It is noted that in the pivotal Phase II studies of Adcetris administered at a dose of 1.8 mg/kg every three weeks 102 patients with Hodgkin's lymphoma and 58 patients with systemic ALCL were exposed for a median duration of approximately 27 weeks or nine cycles and 23.5 weeks or seven cycles respectively.

It is to be noted that an additional 141 patients were enrolled in the three Phase I studies including 45 patients in Study 0001, 44 patients in 0002 and 52 patients in 007. Dosages of Adcetris in these studies were 0.1-3.6 mg/kg every three weeks for Study 0001, 0.4-1.4 mg/kg

weekly for the first three weeks of every four-week cycle for 0002 and 1.8 mg/kg every three weeks for 007. The additional 56 patients in study 008 received Adcetris at a dosage of either 1.2 mg/kg or 1.8 mg/kg every three weeks.

In the six completed studies, a total of 261 patients received at least one dose of Adcetris at the proposed label dosage of 1.8 mg/kg every three weeks of which 160 patients were in the Phase II population, 12 patients in Study 0001, 52 patients in Study 007 and 37 patients in 008A. Approximately 55% of the patients in the Phase II population and 45% of patients in the Phase I/II population received > 24 weeks and > 8 cycles of Adcetris.

It is noted that study design for the two Phase II pivotal studies were essentially the same and there were fairly similar requirements in terms of reporting of adverse events for the other studies. Accordingly all adverse events were reported according to investigator assessment together with relevant grading of adverse events according to WHO criteria.

Reviewing the adverse events which occurred in this patient population. For the Phase II population at least one treatment emergent adverse event of any grade was reported for 158 patients or 99% with at least one Grade III or higher TEAE for 92 subjects or 58%. Serious adverse events were reported for 50 patients or 31% and adverse events leading to discontinuation of study treatment for 36 patients or 23%. In addition six patients or 4% in this population died within 30 days of the last dose of Adcetris and 49 patients or 31% died during follow up.

The incidence and severity of TEAEs were generally similar for patients with HL and those with sALCL. In general the first onset of TEAEs was within the first four treatment cycles.

Reviewing the incidence of at least one treatment adverse event of any grade, this was reported for 158 patients or 99% in the Phase II population. The most common of these were peripheral sensory neuropathy in 45%, fatigue in 43%, nausea in 41%, diarrhoea in 34%, pyrexia and upper respiratory tract infection in 31% each, neutropenia in 21% and vomiting in 20%. These events were generally most often Grade I or II with the exception of neutropenia for which Grade III and IV events were reported for 13 and 7% of the patients respectively. Similar patterns and incidence rates of adverse events were reported for HL and ALCL patients with the exception of a higher incidence of upper respiratory tract infections in HL patients.

In relation to the other studies, other than peripheral neuropathy which had a lower incidence in Study 0001 other TEAEs which differed from the Phase II studies were rash in 18% of patients in Study 0002, tachycardia in 11% of patients in 0001 and blurred vision in 11% of patients in 0002. Overall however the incidence and severity of adverse events were fairly similar in the Phase I studies when doses of Adcetris were comparable.

In relation to treatment related adverse events which were considered to be secondary to treatment by the investigator these were noted in 146 patients in the Phase II population or 91% with the most common being peripheral sensory neuropathy, nausea, fatigue, diarrhoea and neutropenia.

Reviewing high grade treatment emergent adverse events, for the Phase II population at least one Grade III or higher TEAE was reported for 92 patients or 58% with those occurring in at least 5% of patients including neutropenia, peripheral sensory neuropathy and thrombocytopenia and anaemia. For the Phase II population 23 patients or 14% had Grade IV TEAEs and seven patients or 4% had Grade V TEAEs. Grade IV TEAEs were reported for at least one patient in this population included neutropenia in 11 patients, thrombocytopenia in five patients and pulmonary embolism in two patients. The Grade V events were recurrent sALCL in three patients, acute myocardial infarction, recurrent Hodgkin's disease, acute renal failure, respiratory failure and sudden death in one patient each.

In relation to death for the Phase II population a total of six or 4% of patients were reported during the safety reporting period of up to 30 days after last dose of treatment. It is to be noted that the recurrent sALCL and respiratory failure deaths were considered to be related to the

primary disease, the acute myocardial infarction and acute renal failure were considered not related to disease and not related to treatment and the relationship between sudden death and disease was unknown. None of the deaths were considered to be related to Adcetris. A total of 49 patients or 31% in the Phase II population died during the follow up period of which 42 were considered by the investigator to be related to disease under study. Among the Phase I/II population other than the pivotal trials a total of nine patients or 3% died during the safety reporting period although none of these were considered to be directly related to treatment.

In relation to serious adverse events for the Phase II population 31% of patients experienced a SAE of which 28% were at least Grade III or higher and 16% had an SAE that was considered to be related to treatment. The most commonly reported SAEs of any grade were abdominal pain, disease progression that is , recurrent sALCL, demyelinating polyneuropathy, pulmonary embolism and septic shock in three patients each or 2%. It is noted that SAEs were reported for a higher percentage of patients with sALCL at 43% than those with HL at 25%. This was possibly due to the overall older median age of patients in the sALCL population and the aggressive nature of T-cell lymphoma. The percentage of patients with Grade III or higher SAEs and SAEs that were considered to be related to treatment were similar between the two patient populations.

In relation to treatment discontinuation and dose modifications for the Phase II population adverse events that led to discontinuation of study treatment was 36 patients or 23% and a dose modification for 79 patients or 49%. It is noted that the most common reasons for treatment discontinuation were peripheral neuropathy and neutropenia with peripheral neuropathy the most frequent cause of dose modification.

8.1. Considering individual toxicities of importance

Approximately half of the patients in the Phase II studies 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 studies. 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.

1. 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 33-39% had at least one post-baseline ATA+ result and 4-11% 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.

No relevant post-marketing experience is yet available to the TGA evaluator for Adcetris for the proposed indications.

8.2. Evaluator comments

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.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

9.1.1. 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 1-13 excluding transplant. Also 72 patients had received one line of therapy post-ASCT and 49% multiple lines of treatment post-ASCT ranging from 2-11. 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 5/9 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.

9.1.2. 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 1-6 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.

9.2. First round assessment of risk

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.

9.3. 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.

10. 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.

11. Clinical questions

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

12. Second round evaluation of clinical data submitted in response to questions

12.1. Efficacy

Updated information on progression free survival, overall survival data for the two pivotal Studies 0003 in refractory Hodgkin's lymphoma and 0004 in 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.

12.1.1. 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.

12.2. 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% - 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 10-25%. 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.

12.2.1. 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.

13. 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.

13.1. Second round assessment of risks

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.

13.2. Second round assessment of benefit/risk balance

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

14. 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.*

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