A phase 1b clinical trial of the CD40-activating antibody CP-870,893 in combination with cisplatin and pemetrexed in malignant pleural mesothelioma

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Received 15 May 2015; revised 14 August 2015; accepted 11 September 2015

Background: Data from murine models suggest that CD40 activation may synergize with cytotoxic chemotherapy. We aimed to determine the maximum tolerated dose (MTD) and toxicity profile and to explore immunological biomarkers of the CD40-activating antibody CP-870,893 with cisplatin and pemetrexed in patients with malignant pleural mesothelioma (MPM).

Patients and methods: Eligible patients had confirmed MPM, ECOG performance status 0–1, and measurable disease. Patients received cisplatin 75 mg/m² and pemetrexed 500 mg/m² on day 1 and CP-870,893 on day 8 of a 21-day cycle for maximum 6 cycles with up to 6 subsequent cycles single-agent CP-870,893. Immune cell subset changes were examined weekly by flow cytometry.

Results: Fifteen patients were treated at three dose levels. The MTD of CP-870,893 was 0.15 mg/kg, and was exceeded at 0.2 mg/kg with one grade 4 splenic infarction and one grade 3 confusion and hyponatraemia. Cytokine release syndrome (CRS) occurred in most patients (80%) following CP-870,893. Haematological toxicities were consistent with cisplatin and pemetrexed chemotherapy. Six partial responses (40%) and 9 stable disease (53%) as best response were observed. The median overall survival was 16.5 months; the median progression-free survival was 6.3 months. Three patients survived beyond 30 months. CD19+ B cells decreased over 6 cycles of chemoimmunotherapy (P < 0.001) with a concomitant increase in the proportion of CD27+ memory B cells (P < 0.001) and activated CD86+CD27+ memory B cells (P < 0.001), as an immunopharmacodynamic marker of CD40 activation.

Conclusions: CP-870,893 with cisplatin and pemetrexed is safe and tolerable at 0.15 mg/kg, although most patients experience CRS. While objective response rates are similar to chemotherapy alone, three patients achieved long-term survival.

Australia New Zealand Clinical Trials Registry number: ACTRN12609000294257.

Key words: clinical trial, phase I, immunotherapy, CD40, malignant mesothelioma

Introduction

Agonistic anti-CD40 can synergize with chemotherapy and cure advanced tumours in mice [1]. In order to test such combinations in patients, it is essential to first understand if an agonistic anti-CD40 antibody can be safely administered with chemotherapy and to begin to understand what immunobiological changes are induced. CD40 activation may be effective post-chemotherapy through activating dendritic cells that have become ‘loaded’ with antigen from drug-induced tumour cell death, inducing expression of costimulatory molecules CD80 and CD86 and increased production of IL12 among other cytokines [2]. CD40 provides a ‘licence-to-kill’ signal for CD8 T cells, the main effector in immune-mediated tumour regression.

CP-870,893 is a fully human IgG2 antibody which is agonistic for the CD40 receptor. The single-agent maximum tolerated dose (MTD) is 0.2 mg/kg, with dose-limiting toxicities (DLT) of thromboembolic disease and headache. Grade I–II cytokine release syndrome (CRS) is the most common adverse event and partial responses were observed in melanoma and pancreatic...
cancer [3, 4]. A study combining CP-870,893 with carboplatin and paclitaxel estimated an MTD of 0.2 mg/kg for study drug [2].

As malignant pleural mesothelioma (MPM) is only modestly sensitive to chemotherapy with few long-term survivors [5, 6] and given that experimental MPM can be cured by this combination in mice, it represented an ideal tumour in which to determine the MTD of CP-870,893 in combination with cisplatin and pemetrexed when given as first-line therapy.

**patients and methods**

**design**
Prospective, single-centre, phase Ib trial of cisplatin and pemetrexed with CP-870,893. A 3 + 3 phase 1 design was used with a six-patient expansion cohort at the MTD. The primary end point was the MTD of CP-870,893.

Secondary end points included toxicity (NCI CTC Version 3.0), objective tumour response as measured by the modified RECIST criteria [7] and by fluorodeoxyglucose positron emission tomography (FDG-PET) [8], time to progression (TTP), and overall survival (OS).

**eligibility**
Eligible patients had confirmed MPM, Eastern Co-operative Oncology Group (ECOG) performance status (PS) 0–1, and were planned for first-line cisplatin/pemetrexed. All had adequate haematological, renal, and hepatic function and measureable disease (defined by Modified RECIST) [7]. Patients were ineligible if they had previous therapy for MPM, radiotherapy to all measurable lesions, symptomatic central nervous system involvement, or previous malignancy within 10 years. Exclusions specific to study drug were: history of venous thromboembolism or severe autoimmunity. Protocol approved by the Institutional Human Research Ethics Committee and participants provided written informed consent. Australia New Zealand Clinical Trials Registry number ACTRN12609000294257.

**treatment**
Patients received cisplatin 75 mg/m² and pemetrexed 500 mg/m² on day 1 of a 21-day cycle to maximum 6 cycles with vitamin B12 and folate supplementation. CP-870,893 was given on day 8, at three dose levels in consecutive 21-day cycles to maximum 6 cycles with vitamin B12 and folate supplementation. CP-870,893 was stopped on progression or toxicity. Dose-escalation cohort mandated dose de-escalation, with one DLT in a cohort mandating grade 3 haematologic adverse event, despite optimal supportive care, grade 4 lymphopenia if adverse event, despite optimal supportive care, grade 4 haematologic adverse event, or grade ≥3 CRS/acute infusion reaction. More than one DLT in three-patient cohort mandated dose de-escalation, with one DLT in a cohort mandating expansion to six patients. CP-870,893 was initially administered as slow intravenous (IV) bolus in normal saline over 2–6 min, with 25 ml flush. Administration was changed to 30 min in 25 ml normal saline with 100 ml flush after infusion site thrombophlebitis was observed in cohort 1. Patients received premedication with loratadine 10 mg PO, ranitidine 50 mg IV, and paracetamol 1 g PO on day 8, 30–60 min before CP-870,893 administration. Prophylactic medications for chemotherapy included corticosteroids (days −1 to 2) and antiemetics; other anti-cancer treatments were not allowed. Chemotherapy was stopped before six cycles in the event of progression, unacceptable toxicity, or patient withdrawal; in this event, CP-870,893 was also stopped. Patients with stable or responding tumour at six cycles could continue single-agent CP-870,893 for a further six cycles at the same dose level. CP-870,893 was stopped on progression or toxicity. Dose-escalation cohort patients were reviewed clinically weekly during combination treatment, and 3-weekly while on CP-870,893 only. Expansion cohort patients were reviewed 3-weekly. Complete blood count, hepatic and renal function tests, and toxicity assessment were carried out weekly on combination treatment and 3-weekly on CP-870,893 alone.

**response assessment**
History and examination were required at baseline, and day 1 of each cycle. A thoracoabdominal CT scan was carried out at baseline, then weeks 6, 12, and 18, and 12-weekly thereafter. Radiological responses were assessed using RECIST modified for mesothelioma [7]. Patients without previous talc pleurodesis had an FDG-PET scan at baseline and before cycle 2. FDG-PET imaging was carried out on a Siemens Biograph-16 PET-CT. Visual and quantitative analyses using total glycolytic volume (TGV) were applied. Response criteria were as previously reported [8]. Serum mesothelin was measured by ELISA (Fujirebio, Malvern, PA) [9].

**time-to-event end points**
TTP was measured from enrolment to progression or death. Response duration was measured from PR to progression or death. Survival was measured from enrolment until death. Toxicity grading used the National Cancer Institute (NCI) Common Toxicity Criteria AE, version 3.0.

**correlative biomarkers**
Serum for mesothelin was collected at baseline, weeks 6, 12, and 18, and 12-weekly thereafter and stored at −80°C. Whole blood for peripheral blood mononuclear cell (PBMC) isolation was collected into BD K2EDTA Vacutainers (BD Diagnostics, Australia) weekly during combined treatment (days 1, 8, 15), always before treatment administration. PBMC were isolated by Ficoll-Paque™ density gradient centrifugation, and cryopreserved in liquid nitrogen until analysis. Dual baseline samples were collected within 14 days of day 1, and pre-treatment on day 1 cycle 1.

Serial analyses were carried out on cryopreserved PBMCs, with all samples analysed concurrently for individual patients ensuring comparable experimental conditions across timepoints. PBMCs were thawed for 1 min at 37°C and washed once in RPMI (Invitrogen), followed by two washes in PBS. Dead cells were identified using LIVE/DEAD Fixable Aqua Dead Cell Stain Kit (Molecular Probes, Eugene, OR). B cells were identified from lymphocytes as staining with CD19-BV421, and negative for a lineage cocktail (lin−) of CD3–BV510, CD14–BV510, and CD56–BV510 (all Biolegend, San Diego, CA). B-cell subpopulations were identified by CD27–APC-H7 (BD Biosciences, San Jose, CA) and CD86–APC (Biolegend, San Diego, CA). Samples were run on a FACSCanII flow cytometer using FACSDiva software (both BD Biosciences). At least 50 000 lymphocyte events were collected per sample. Data were analysed using FlowJo software (Tree Star Inc., Ashland, OR), gated as per supplementary Figure S1, available at *Annals of Oncology* online.

**immunohistochemistry**
Immunohistochemistry was carried out on 4 µm-thick formalin-fixed paraffin-embedded core biopsy sections using an Autostainer Link 48 (Dako, Copenhagen, Denmark). Rehydration and antigen-retrieval steps were carried out in a PT Link pre-treatment module (Dako) using EnVision™ FLEX+ Target Retrieval Solution, High pH (Dako). B cells were identified using a mouse monoclonal antibody against CD20 (clone J5B117, Dako).

**statistical considerations**
Time to event end points were analysed using the Kaplan–Meier method. Linear mixed models were used to analyse the relationship between time and
lymphocyte subsets, in addition to testing for interaction. Analysis used the R environment for statistical computing and SPSS for Windows statistical package version 17.0.

results

patient characteristics

Sixteen patients were enrolled between March 2010 and October 2011; one withdrew before receiving treatment and is excluded from analysis. Minimum follow-up is 22 months. Patient characteristics are shown in Table 1. All patients had radiologically assessable disease; 12 had no prior pleurodesis and were eligible for FDG-PET assessment.

treatment delivered

Ninety-two cycles of CP-870,893 were given, 24 (26%) at dose level 0.1 mg/kg (n = 3 patients + one de-escalated from 0.2 mg/kg), 8 (9%) at 0.2 mg/kg (n = 3 patients), and 60 (65%) at 0.15 mg/kg (n = 9 patients). Patients received a median of four cycles of CP-870,893 (range 2–12). Patient 3 on dose level 2 received one dose at 0.2 mg/m² and was de-escalated to the established safe dose of 0.1 mg/m² following development of DLT in two other patients at that level. One patient received a dose reduction from 0.15 to 0.1 mg/kg following an episode of grade III CRS.

Seventy-one cycles of cisplatin and pemetrexed were given (median 5 cycles, range 2–6). No dose reductions were required, with the median dose intensity 100%. Patient 1 changed from cisplatin to carboplatin after four cycles due to sensorineural hearing loss.

toxicity

Haematological toxicity, emesis, and fatigue were consistent with reported chemotherapy toxicities (Table 2). No significant renal toxicity, hepatic toxicity, or stomatitis was observed. Four patients developed superficial thrombophlebitis at sites of CP-870,893 administration, recurring in some patients.

Thirteen patients experienced CRS at least once. Onset was within 15 min to 3 h, symptoms including rigors, fever, myalgias, nausea, and vomiting. Maximum grade was 3 in 2 patients; 2 in 10 patients; and 1 in 1 patient. Symptoms abated rapidly following treatment with promethazine, lORazepam SL, pethidine, and metoclopramide, used for all grade 2 or higher reactions. The two patients with grade 3 CRS experienced this on cycles 1 (of 6) and 2 (of 4), respectively, neither having subsequent recurrence of grade 3 toxicity.

Six serious adverse events were reported, four attributed to CP-870,893. One patient treated at 0.2 mg/kg developed hepatic vein thrombosis and splenic infarction shortly after the fourth dose of study drug (reported as two SAEs), with a similar abdominal pain event of lower severity managed at a peripheral hospital during the previous cycle. A patient with mild baseline hyponatraemia (sodium 130 mmol/l) developed asymptomatic grade 3 hyponatraemia within 24 h of study drug administration on day 8 cycle 3. Hyponatraemia resolved to baseline, but grade 3 hyponatraemia recurred, accompanied by grade 3 confusion after CP-870,893 administration in cycle 4. A third patient with cardiac risk factors was admitted for ischaemic chest pain during a CRS episode. Two tumour-related SAEs were for chest pain and chest infection.

treatment response

Six patients (40%) had a partial response and eight (53%) stable disease as best radiological response, with one (7%) progressive disease at first assessment (Figure 1A). Patient 1 displayed the greatest reduction in tumour burden (Figure 1B). To date, 12 of 15 participants are deceased, all deaths from mesothelioma. The median OS is 16.5 (95% CI 5.1–28.1) months (Figure 1C). The median progression-free survival was 6.3 (95% CI 2.3–10.3) months (Figure 1D). Patients 1, 2, and 12 are long-term survivors, with survival of 44, 44, and 31 months, respectively, from study start.

Of patients eligible for PET assessment, qualitative reports described partial response (n = 5, 33%) (supplementary Figure S2, available at Annals of Oncology online), stable disease (n = 6, 40%), and two mixed responses (13%). TGV changes between baseline and end of cycle 1 ranged from −62% to −9% of baseline. Changes in SUVmax between baseline and end of cycle 1 ranged from 28% to 54%.

**Table 1.** Patient demographics and baseline characteristics for 15 eligible patients

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**Table 2.** Adverse events occurring in all patients, all grades, all courses

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<td>3</td>
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from −38% to +16% of baseline. Patients assessed as a qualitative partial response had TGV changes ranging between −48% and −62% of baseline, with corresponding SUVmax changes between −16% and −38% of baseline. Response findings from CT and FDG-PET were consistent.

**mesothelin**

The median serum mesothelin concentration at baseline was 3.8 nM (range 1.1–30 nM), 10 patients having levels above the upper normal threshold (i.e. 2.5 nM). There was no association between baseline mesothelin concentrations and response or

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**Figure 1.** (A) Maximum per cent reduction in target lesions in patients assessable for radiological response; (B) illustrative durable response from patient 1, treated at 0.1 mg/kg, showing baseline and 41 months following study entry (most recent imaging); (C) overall survival from start of treatment; (D) time to progression from start of treatment; (E) serum mesothelin levels at baseline (B) and nadir (N) categorized [as partial response (PR), stable disease (SD) or progressive disease (PD)] by radiological response; (F) overall survival analysed by change from baseline in mesothelin level.
survival. There was a significant correlation between radiological response and change between baseline and nadir mesothelin concentrations ($r_c = 0.587; P = 0.022$). Changes between baseline and nadir mesothelin levels predicted for survival, with significant survival differences between those with decreased, stable, or increased mesothelin (Figure 1E and F).

**immunological biomarkers**

All lymphocyte subset parameters showed a marked cyclical pattern, in keeping with haematological changes induced by chemotherapy alone (Figure 2). The goal of analysis was to investigate longitudinal change over 6 cycles, independent of this wide but reproducible variability within individual cycles. In a linear mixed model, there was a decreasing relationship between time and the B-cell ($CD19^+$) proportion of total lymphocytes ($P < 0.001$; Figure 2A). The proportion of memory B cells ($CD27^+$) increased by almost 50% over six cycles ($P < 0.001$; Figure 2B), with a concomitant increase in the proportion of those memory B cells expressing the activation marker CD86 ($P < 0.001$; Figure 2C).

Although B-cell parameters showed changes over the entire chemoimmunotherapy course, changes within a single treatment cycle reflected the cyclical haematopoietic response to chemotherapy. The mean proportion of $CD19^+$ lymphocytes decreased from days 1 to 8 ($P = 0.048$) and again from days 8 to 15 ($P < 0.001$), before a rebound increase between days 15 and 21 ($P < 0.001$) before the subsequent chemotherapy cycle (Figure 2A). $CD27^+$ memory B cells showed a reversed pattern, with an increase from days 1 to 8 ($P = 0.002$), a further increase from days 8 to 15 ($P = 0.008$), and a decrease from days 15 to 21 ($P < 0.001$) which did not return to baseline, allowing an ongoing upward trajectory (Figure 2B). The pattern for CD86 expression was different, with a sharp decrease in the proportion of CD86-expressing B cells between days 1 and 8 ($P < 0.001$), a rapid rebound to just above baseline between days 8 and 15 ($P < 0.001$), and no significant change between days 15 and 21 ($P = 0.95$) (Figure 2C).

**pre- and post-treatment biopsies**

Two patients in the expansion cohort had a pre-treatment diagnostic biopsy available, and a post-treatment biopsy taken in the third week of cycle 2. Mild B-cell infiltration was observed in both pre- and post-treatment biopsies (supplementary Figure S3, available at *Annals of Oncology* online).

**discussion**

Given the clear preclinical synergism between chemotherapy and activating anti-CD40 antibody therapy, and the compelling scientific rationale for the combination, it is crucial to understand how anti-CD40 can be safely administered with chemotherapy and to demonstrate that chemotherapy does not abrogate the immunopharmacodynamic evidence of CD40 activation. This phase Ib study demonstrates how combination of chemoimmunotherapy with cisplatin/pemetrexed and CD40 activation using CP-870,893 can be used, and shows a small proportion of extremely long-term survivors after treatment. Importantly, the addition of CP-870,893 to chemotherapy did not compromise the ability to deliver standard treatment, with 100% dose intensity of cytotoxic drugs and a pattern of chemotherapy-related toxicities consistent with expectations.

Here, we report an MTD of CP-870,893 with cisplatin–pemetrexed of 0.15 mg/kg, lower than two recent studies which determined an MTD of 0.2 mg/kg, equal to the single-agent dose, with either single-agent gemcitabine or combination carboplatin/paclitaxel [2, 10]. Both DLTs in this study at 0.2 mg/kg demonstrated a clear relationship to study drug, occurring within 24 h of study drug infusion at an initial lower grade, and with increased severity on re-administration of CP-870,893. A key difference between the present study and these previous studies is that the MTD was defined in the published reports as the highest dose level at which ≥2 of 6 patients experienced DLT during cycle 1, whereas DLT were considered across the entire treatment course in our study. Thromboembolic events appear prominent with this agent, with one of the 13 patients treated at 0.2 mg/kg with carboplatin/paclitaxel developing a fatal cerebrovascular accident, and another an optic nerve infarction that was not considered a DLT [2]. Combination with gemcitabine also noted one cerebrovascular accident within 24 h of study drug infusion [10]. One DLT on the present study was a thromboembolic event occurring in cycle 2 and recurred at higher grade in the fourth cycle. Mechanistically, platelets express CD40L and may mediate the thrombotic process [11]. As both DLTs on the present study occurred in later treatment cycles, our study would have expanded the cohort at 0.2 mg/kg had we used the alternative definition of DLT. Given the seriousness of thromboembolic events described in all three studies at 0.2 mg/kg, as well as the onset after the first cycle, we contend that a dose of 0.2 mg/kg may not have an acceptable safety profile in patients on chemotherapy when repeated dosing is used. Further studies and increased patient numbers will better characterize the incidence of thromboembolic events.

Although the sequence of administration of chemotherapy and anti-CD40 was important in animal studies, it is difficult to extrapolate an appropriate dosing schedule to clinical trials. We selected day 8 immunotherapy administration with the rationale that this would allow for recovery from acute chemotherapy toxicities, and could potentially generate an immune response that could skew towards anti-tumour reactivity during homeostatic proliferation. Studies by Vonderheide and Beatty also included alternative scheduling. Vonderheide et al. administered study drug on two schedules, day 3 or day 8 following day 1 chemotherapy. Beatty et al. administered study drug on day 3 of a 28-day cycle with gemcitabine. Importantly, there were no differences in immune pharmacodynamics, toxicity, or activity between days 3 and 8 schedules with carboplatin and paclitaxel, suggesting that our day 8 schedule is unlikely to be responsible for differences between studies in MTD or immunological biomarkers [2].

The most frequent additional toxicity to chemotherapy was CRS. CRS with CP-870,893 has been well characterized, and is associated with increased serum TNF-α and IL-6 [12]. The clinical pattern was similar to previously reported and required patient and nursing staff education for early management. Although CRS represents a measurable biological effect of CP-870,893, changes in immune parameters, particularly lymphocytes, would potentially be of greater prognostic significance.
Figure 2. Longitudinal flow cytometry data in B cells across six cycles of chemoimmunotherapy, for (A) the B-cell (CD19+) proportion of total lymphocytes; (B) memory cell (CD27+) proportion of total CD19+ B cells; and (C) the activated (CD86+) proportion of CD27+CD19+ memory B cells. Left-hand panels show observed values from individual patients, together with their empirical means (solid line), mean, and SD at baseline are quoted. Values printed above the X-axes represent the number of treatment cycles undertaken, values below the X-axes denote the treatment day within that particular cycle (i.e. day 1, day 8, or day 15). Timepoint ‘B’ represent pre-study baseline samples. Centre panels show results of fitting a linear mixed model; a linear trend over time and additive treatment effects of the day of the treatment yield the corresponding population average curves. Average change over the duration of the study is described. Right-hand panels show estimated treatment means, showing differences between day 1, day 8, and day 15 of the chemoimmunotherapy treatment over 6 cycles. (P-values: * <0.05, ** <0.01, *** <0.001.)
The observation that general immune parameter changes do not reliably predict outcome is consistent with a body of work in immunotherapies such as checkpoint blockade. Such studies have not yet identified peripheral blood biomarkers of immune activation and response that could be simply applied in routine clinical practice. These findings support the need to identify tumour neo-antigens in each patient to use for tracking tumour-specific responses which has proven so valuable in tracking anti-tumour responses in animals receiving chemotherapy and anti-CD40 [1], and which is now becoming possible via exome sequencing [13].

While it is unlikely to be practical for a multicentre randomized trial, early work with immunoreactive drugs must consider intensive analysis of immune biomarkers at daily or weekly timepoints early in drug development, or risk being unable to identify relevant biomarkers. In a previous CP-870,893 single agent repeated weekly dosing study, some patients demonstrated a decrease in absolute CD3+, CD4+, and CD8+ T-cell counts at the end of treatment relative to baseline [4]. B cells have also been demonstrably affected, with very early alterations in B-cell parameters marking a pharmacodynamic effect; an acute decrease in the numbers and proportion of circulating B cells in whole blood over 72 h following the infusion, returning to baseline by day 8, given as monotherapy or with carboplatin and paclitaxel [2, 12]. Activation of dendritic cells is thought to be a primary mechanism behind anti-CD40 therapy, with DC subsequently able to ‘licence’ CD8+ T-cells to carry out tumour-killing activity—however, B cells also express CD40 and can play an antigen-presenting role [14]. Cyclic lymphocyte changes with chemotherapy pose challenges to interpreting the immunological pharmacodynamics of chemoimmunotherapy combinations. Our intent was to identify patterns of longitudinal change over an entire treatment course. In keeping with previous studies, we examined the overall (CD19+) B-cell proportion of peripheral blood lymphocytes in response to treatment, using CD27 as a marker to distinguish between naïve (CD27−) B cells and those with a differentiated, memory (CD27+) phenotype. Memory B cells arise predominantly in germinal centres in the spleen and lymph nodes as a result of T-cell-dependent antigen response, and can further differentiate to antibody-secreting plasma cells upon subsequent antigen recognition—reviewed in [15]. We also examined expression of the activation marker CD86, which is expressed at higher levels and modulated more strongly in memory rather than naïve B cells. Using statistical mixed models, we demonstrated significant changes in the B-cell compartment, memory, and activation markers which are consistent with the previous literature but over the longer term [2, 4, 11]. This suggests that while combination administration with chemotherapy allows cyclical return towards baseline, the immunopharmacodynamic effect of CP-870,893 is not abrogated by combination with chemotherapy. The observed decrease in CD19+ B cells over the treatment course is consistent with the reported transient decrease after anti-CD40 administration, although chemotherapy appears to contribute to this effect in the first week of each cycle [4]. An overall increase in CD27+ memory B cells suggests increased stimulation in response to antigen, and increased CD86 expression has been previously documented in response to CP-870,893 [16]. However, a chemotherapy-only control group would be required to conclusively demonstrate that these effects are not seen with standard treatment, which was beyond the scope of this study. The presence of tumour-infiltrating B cells in pre- and post-treatment biopsies would theoretically allow for B cells to perform an antigen-presenting role within the tumour microenvironment throughout treatment; whether or not this is the case requires further investigation.

Finally, this study has shown a signal for efficacy that is in keeping with other immunotherapy studies; notably, a small proportion of long-term survivors, one of whom did not required additional treatment for 44 months following study enrolment. Although the study design was not primarily to test efficacy, many tumour responses were profound. No evidence of prolongation of TTP over historical data was seen, but this may have been affected by the response criteria used, as the study protocol pre-dated the development of immune-related response criteria and no allowance was made for continuation of treatment through progression or the development of discordant responses. Had the protocol allowed for continuation of therapy, some progression events may have been considered in keeping with immunological pseudoprogression. Examples include the withdrawal of patient 1, a subsequent long-term responder, following development of a symptomatic increased pleural effusion during monotherapy; and withdrawal of another participant following development of a pericardial effusion which subsequently resolved.

In conclusion, the combination of cisplatin/pemetrexed and CP-870,893 at 0.15 mg/kg 3-weekly is tolerable and shows efficacy at least that expected from chemotherapy alone. This combination warrants testing in a randomized clinical trial, ideally with additional exploration of scheduling and immunological biomarkers.

Acknowledgements
This study was supported in part by a grant from Pfizer Oncology Australia partially funding data management and providing CP-870,893. Laboratory analyses were supported by a grant from Cancer Council Western Australia. The investigators wish to acknowledge the data management staff, in particular Ms Judy Innes-Rowe and Ms Hema Rajandran. We also acknowledge the assistance of other research staff in sample processing and Charley Budgeon for statistical assistance. The authors acknowledge the facilities, and the scientific and technical assistance of the Australian Microscopy & Microanalysis Research Facility at the Centre for Microscopy, Characterisation & Analysis, the University of Western Australia, a facility funded by the University, State and Commonwealth Governments.

Funding
This work was supported by Pfizer Oncology Australia; The Cancer Council Western Australia (grant number 1028735); National Health and Medical Research Council of Australia (grant number 458543); and the Insurance Commission of Western Australia.

Disclosure
The authors have declared no conflicts of interest.
references


Allogeneic stem-cell transplantation in patients with cutaneous lymphoma: updated results from a single institution

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Received 2 June 2015; revised 20 August 2015; accepted 18 September 2015

Background: Cutaneous T-cell lymphomas (CTCLs) and its common variants mycosis fungoides (MF) and leukemic Sézary syndrome (SS) are rare extranodal non-Hodgkin’s lymphomas. Patients who present with advanced disease and large-cell transformation (LCT) are incurable with standard treatments. In this article, we report the largest single-center experience with allogeneic stem-cell transplantation (SCT) for advanced CTCL.

Patients and methods: This is a prospective case series of 47 CTCL patients who underwent allogeneic SCT after failure of standard therapy between July 2001 and September 2013. The Kaplan–Meier method was used to estimate overall survival (OS) and progression-free survival (PFS) curves. The method of Fine and Gray was used to fit regression models to the same covariates for these cumulative incidence data.

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