Final results of the DREAM trial: A Phase 2 trial of durvalumab with first-line chemotherapy in mesothelioma with a safety run-in

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Summary

Background

Chemotherapy with cisplatin and pemetrexed improves survival in malignant pleural mesothelioma (MPM). This study evaluated durvalumab, an anti-PD-L1 (programmed death ligand-1) antibody, given during and after first line chemotherapy with cisplatin and pemetrexed durvalumab in advanced MPM.

Methods

DREAM was a single-arm, multicentre, open-label phase 2 trial in adults with treatment-naive, advanced MPM. Eligible patients had an Eastern Cooperative Oncology Group performance status 0 or 1 and measurable disease. The first six participants were treated for two cycles in a safety run-in. All participants received cisplatin 75mg/m^2, pemetrexed 500mg/m^2, and durvalumab 1125mg intravenously on day 1 of a three-weekly schedule for a maximum of six cycles chemotherapy. Change from cisplatin to carboplatin AUC5 was permitted. Durvalumab was continued for a maximum total of 12 months. The primary endpoint was progression-free survival at six months (PFS6) measured according to modified RECIST for MPM and analysed by intention-to-treat. (ACTRN12616001170415).

Findings

Fifty-four participants were enrolled between 28 December 2016 and 27 September 2017. Most were male (83%), with epithelioid subtype (83%), and a median age of 68 years. In the final analysis, with a median follow up of 28.2 months (IQR 26.5-30.2). 31 (57.4%) of 54 patients were alive and progression-free at six months (95% CI 44-70%). The most common grade 3-4 adverse events were gastrointestinal in 15 (28%) of 54 participants and laboratory abnormalities in 9 (17%) of 54 participants. A total of 60 serious adverse events occurred in 29 participants. None of the five deaths during study treatment were attributed to study treatment.

Interpretation

This single-arm phase 2 trial demonstrated that the combination of durvalumab, cisplatin, and pemetrexed has promising activity and safety that warrants the conduct of a randomised phase 3 trial.

Funding

AstraZeneca provided study drug and funding. However, the design, conduct, analysis, reporting and interpretation of the study results were independent of AstraZeneca.

Research in context

Evidence before this study

We searched Medline database for reports from 1st January 2006 to 31st December 2019 using the terms “mesothelioma”, “checkpoint blockade”, OR “Programmed Cell Death 1 receptor”, and “antineoplastic combined chemotherapy protocols”, and filtered by clinical trials. There are no previous published clinical reports of combination immune checkpoint inhibitor (ICI) and chemotherapy in mesothelioma. Early single-arm, single-agent studies of ICI in mesothelioma have demonstrated modest objective responses. Combination ICI provides possible small incremental benefits in phase 2 and non-comparative trials (Level 2b evidence). In other cancers, such as non-small cell lung cancer (NSCLC), combinations of chemotherapy and ICI have recently demonstrated benefits in OS (Level 1b evidence). This trial was developed in the context of extensive laboratory data suggesting the potential for benefit of combined chemotherapy and immunotherapy, including ICI.

Added value of this study

This is the first clinical trial report combining ICI with standard chemotherapy in mesothelioma. This study met its primary endpoint, identifying a promising signal for efficacy in PFS. Objective responses were seen at a frequency over that expected for chemotherapy alone. Safety data are consistent with those expected for a combination of chemotherapy and ICI. Five deaths occurred during study treatment, all were judged as unrelated to durvalumab. There was no apparent correlation between tumour expression of PD-L1 and outcomes.

Implications of all the available evidence

This study provides the first information on the combination of ICI with chemotherapy in mesothelioma. These results support initiation of a randomised phase 3 trial to determine the effectiveness of this combination in this setting.

Introduction

Standard first-line chemotherapy for mesothelioma consists of up to six cycles cisplatin and pemetrexed, with a survival benefit of approximately three months over cisplatin alone, and benefits to quality of life.[1] Carboplatin can be used where cisplatin is contraindicated or toxicities develop.[2] Adding bevacizumab to chemotherapy demonstrated modest survival benefit in one study,[3] while other Vascular Endothelial Growth Factor (VEGF)-based strategies have not.[4] Patients invariably develop disease progression once treatment stops. There is a strong unmet need for improving systemic therapy in mesothelioma.

Immune checkpoint inhibitors (ICI) are an emerging treatment in mesothelioma. While anti-Cytotoxic T Lymphocyte Antigen-4 (CTLA-4) therapy did not show any benefit over placebo,[5] there is demonstrable activity of single-agent anti- Programmed Cell Death 1 (PD-1) and Programmed Cell Death Ligand 1 (PD-L1) antibodies[6-9] and of dual ICI.[10-12] Durvalumab has not been tested as a single agent in mesothelioma. While mesothelioma expresses PD-L1, the relationship between ICI efficacy and PD-L1 expression is not clearly defined, nor are the ideal assays and cut points.[6,7]

Findings from our team and others have shown that chemotherapeutics can have beneficial immune-stimulating properties in mesothelioma models;[13-15] in particular, for platinum-based chemotherapy.[16] Recent positive clinical trials in small cell lung cancer and non-small cell lung cancer (NSCLC) support combining chemotherapy with immunotherapy.[17,18]

Here, we present results from the DREAM study (ACTRN12616001170415), a multi-institution single-arm phase 2 trial that aimed to evaluate the activity of the combination of cisplatin, pemetrexed, and durvalumab in patients with no prior systemic therapy for malignant pleural mesothelioma (MPM).

Methods

Study design and participants

This was a multicentre, Australian, single-arm phase 2 trial with a safety lead-in of 6 participants. Participants were adults aged 18 years or older, with histologically confirmed MPM considered unsuitable for cancer-directed surgery, and previously untreated with systemic therapy for MPM. All histological subtypes were eligible. Participants required available archival tissue for correlative studies, measurable disease as per modified RECIST for mesothelioma (mRECIST),[19] with no prior radiotherapy to lesions which were being

measured; Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1; and, adequate haematological, hepatic and renal function including creatinine clearance > 60mL/min. Patients with any prior chemotherapy, immune checkpoint blockade, or systemic anticancer therapy for MPM, and those with treatment with investigational products within the previous 12 months were excluded. People with pre-existing hearing loss or peripheral neuropathy, uncontrolled intercurrent illness, active auto-immune disease, another malignancy within 5 years prior to enrolment, or those with a life expectancy of less than 24 weeks were excluded. Patients with interstitial lung disease or requiring more than adrenal replacement dose corticosteroids were excluded.

DREAM conformed to ethical principles of the Declaration of Helsinki and the International Council on Harmonization guidelines on Good Clinical Practice. The protocol was approved by a central Human Research Ethics Committee (HREC), and all site HRECs. All patients provided written informed consent before any screening procedures. Patients confirmed eligible after screening were registered to the study.

Procedures

All participants began treatment with cisplatin 75mg/m^2, pemetrexed (Eli Lilly, Indianapolis, USA) 500mg/m^2, and durvalumab (AstraZeneca, Frederick, USA) 1125mg (fixed dose), all given intravenously on the same day, and repeated every 21 days for a maximum of 6 cycles. The durvalumab dose of 1125mg every 3 weeks was chosen to give the same dose intensity (375 mg per week) as the then-standard recommended dose of 1500mg every 4 weeks, to improve convenience and acceptability. Supplementation with folic acid 0.5mg daily and Vitamin B12 1000IU every nine weeks commenced at least one week before chemotherapy administration and continued during chemotherapy. Supportive measures including antiemetics, peri-chemotherapy corticosteroids, hydration protocols, and analgesia was provided according to local institutional guidelines. Participants developing cisplatin-induced hearing loss, renal impairment, or hypersensitivity could switch cisplatin to carboplatin with an area under the curve (AUC) of 5. Other indications for switching to carboplatin were discussed case-by-case with the study chair. Criteria for retreatment, dose delays, dose modifications, and stopping cessation of chemotherapy were described in the protocol. No dose reductions were allowed for durvalumab, however durvalumab could be withheld pending resolution of immune-related adverse events (irAEs) to ≤ grade 1 or baseline, and restarted. Dose reductions of platinum and/or pemetrexed to 75% and 50% of baseline were required for

specific toxicity scenarios. If permanent discontinuation of chemotherapy for reasons other than progression was required before completing six cycles, then durvalumab could be continued. A total of 39 protocol deviations were recorded on trial, all minor with no protocol violations or serious breaches. There were no protocol amendments impacting trial recruitment or conduct.

Durvalumab was to be continued as a single-agent for another 12 cycles after completion of chemotherapy, for a maximum total of 18 cycles (12 months from day 1 cycle 1). Dose modifications of durvalumab were not permitted. Guidelines for management of irAEs were detailed in the protocol. If durvalumab was withheld and chemotherapy continued, then subsequent durvalumab was restarted together with the next administration of chemotherapy when, criteria for recommencement were met.

Clinical assessments were performed at screening, baseline, and then three-weekly during study treatment. Baseline assessments included blood tests for renal and liver function ~~tests~~, haematology, urinalysis, coagulation studies, thyroid function tests, Hepatitis B and C serology, and electrocardiography. Laboratory tests were subsequently performed three-weekly, at end of treatment, and then every 4 weeks through to 90 days from the last dose. Adverse events (AEs) were recorded —from the first dose of study treatment to 90 days following the last dose of study treatment, and were classified and graded according to the NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. Survival status was updated every 3 months after completing study treatment.

Tumour imaging by CT of the chest and upper abdomen was performed at baseline and six-weekly until week 48, then 12-weekly thereafter until disease progression was confirmed. Response and progression were assessed by both mRECIST[19] (for MPM) and modified RECIST 1.1 for immune-based therapeutics (iRECIST).[20] If patients continued treatment beyond progression, and progression was subsequently confirmed, then the date of progression was taken to be the date that criteria for progression were first met. Patients stopped all study treatment following confirmed progression or dose limiting toxicities (DLTs). Post-study treatment was at the discretion of the treating clinician and was not collected.

Outcomes

The primary outcome measure was progression-free survival (PFS) at six months (PFS6), defined as the proportion of patients alive and free of progression (stable disease [SD], partial

response [PR] or complete response [CR]) at the imaging point at 24 weeks from the date of registration. PFS was measured from the date of registration until either date of disease progression or date of death from any cause. The date of first disease progression based on imaging was that of the first scan meeting criteria for progressive disease (PD), even if determined retrospectively in the context of suspected pseudoprogression or unconfirmed progression. Participants who continued treatment beyond initial PD but who subsequently attained PR or CR which was maintained at or beyond six months from registration were considered to have attained PFS6. For patients alive and progression-free at the final analysis date, PFS was censored at the most recent tumour assessment date. Participants who died without prior progression were considered to have progressed on the date of death. Participants who started subsequent anti-cancer therapy without prior reported progression were considered to have progressed at that date. PFS6 was centrally reviewed using investigator-determined tumour measurements.

Secondary endpoints included objective tumour response rate (RR), frequency and severity of AEs, and overall survival (OS). OS was defined from date of registration to date of death from any cause. Patients who were alive or lost to follow-up at the time of the final analysis were censored on the last date known alive. The RR was defined as the proportion of participants with confirmed investigator-assessed CR or PR by mRECIST. Analysis was also performed by iRECIST. A confirmed response required a subsequent assessment at least four weeks after the first response observation. Tertiary endpoints included associations between clinical outcomes via both iRECIST and mRECIST and potential correlative laboratory markers, and with the exception of tumour PD-L1 expression, will be reported subsequently.

Archival tumour samples from diagnostic biopsies were assessed centrally for PD-L1 expression by immunohistochemistry using PD-L1 clone SP263 pre-dilute (Ventana cat no. 741-4905, Roche Diagnostics GmbH, D-68305, Mannheim Germany)[21] and visualised using the Ventana three-step detection system OptiView (cat no. 950-224, Ventana Medical Systems, Inc. Tucson, Arizona 85755, USA). An analysis plan was developed *a priori*. PD-L1 expression was assessed as both Tumour Proportion Score (TPS) and Combined Cell Percentage (CCP) using methods recommended in companion diagnostic testing in NSCLC[22] and previously described in mesothelioma,[7] respectively. TPS is percentage of positive staining tumour cells of the total assessable tumour cells, defined as showing any perceptible linear cell membrane staining (partial or complete) in viable tumour cells, excluding any associated immune cells, benign cells, cytoplasmic staining, and necrotic areas. CCP is the percentage of

positive staining in tumour and associated inflammatory cells (tumour infiltrating lymphocytes or histiocytes), excluding any benign cells, pulmonary macrophages, cytoplasmic staining, and necrotic areas. The primary analysis was by positive (TPS ≥ 1%) versus negative (TPS < 1%) PD-L1 expression.[6] For secondary analyses, expression levels were coded as <1%, 1% to <5%, 5% to <50%, and >50%. Expression levels of >5% were also examined as a separate category. The same analyses were applied to CCP. All analyses were pre-specified before examining the data.

Statistical design and analysis

The study began with a safety run-in with real-time reporting of adverse events, do-limiting toxicity, and safety analyses after three and six participants had completed two cycles of treatment. These six participants were assessed and included for all efficacy outcomes using the same schedule and criteria as subsequent participants.

The trial sample size was based on Simon's two-stage minimax design, with stopping rules for futility if the first stage did not meet criteria for study continuation.[23] The null hypothesis was that the true PFS6 was 45%, which would be in keeping with standard therapy. In the first stage if 17 or more of the first 31 eligible participants recruited had progressed or died within six months, then the study was to close for futility, otherwise an additional 23 participants were to be recruited for stage 2. Events for PFS6 were monitored centrally and reviewed in real-time, to allow consideration of early stopping if the stage 1 futility boundary was crossed. If 31 or more of 54 participants recruited in total were alive and progression-free at six months, then the null hypothesis would be rejected in favour of a one-sided alternative that the PFS6 was greater than 45%. This design provided greater than 90% power if the true PFS6 rate was 65% with a one-sided type I error rate of 5%. There was provision for over-accrual to replace ineligible patients. All efficacy analyses were performed by intention-to-treat. Safety analyses included all participants who receive at least one dose of any study drug.

The PFS6 rate and its two-sided 95% confidence interval were estimated using the Kaplan-Meier method. The secondary outcomes of OS and PFS are reported as medians and event-free proportions. The RR is reported as a proportion with a two-sided 95% confidence interval. Safety data is summarised using descriptive statistics, including AEs observed from the beginning of dosing until 90 days after the last dose for each participant. The number of participants experiencing each AE is summarised by the CTCAE V4.03 terminology and grade. Serious AEs, irAEs, and all deaths were summarised separately. Analyses were undertaken in

SAS (version 9.4) and R (version 3.6). This study is registered with the Australia New Zealand Clinical Trials Registry (ACTRN12616001170415).

Role of the funding source

This was an investigator-initiated, academic, cooperative group trial lead by the Australian Lung cancer Trials Group and NHMRC Clinical Trials Centre, and sponsored by the University of Sydney. AstraZeneca provided durvalumab and funding to support trial activities. AstraZeneca reviewed the protocol and study report, but were not involved in the study design, data collection, analyses, interpretation of results, or preparation of the report. The corresponding author had full access to all of the data and the final responsibility to submit for publication. Authors P-S.K, C.B and A.L had access to the raw data. All authors had full access to the data and were involved in preparation of the publication.

Results

Between 28 December 2016 and 27 September 2017, 55 patients were recruited from nine sites (Supplementary Appendix Table 2), but one was deemed ineligible prior to starting treatment due to prolonged QTc interval. All eligible participants were assessable. At the final analysis, 31 (57.4%) of 54 eligible participants were alive and progression-free at six months, meeting the criterion for activity pre-specified in the trial protocol.

Patient demographics and baseline characteristics are presented in Table 1. The median age was 68 years (IQR 61,73), and 45 (83%) of 54 patients were male. 45 (83%) of 54 patients had epithelioid histology. Five (9%) of 54 patients had any prior surgery, none with curative/radical intent, and all had residual measurable disease. Four (7%) of 54 patients had received prior radiotherapy.

No DLTs were experienced in the safety run-in using three-weekly 1125mg durvalumab with standard dose cisplatin and pemetrexed. The same dose and schedule was therefore used for all 54 participants. The study met its pre-specified criteria for continuing recruitment beyond 31 participants to its planned total of 54.

All 54 patients received at least one dose of cisplatin with 13 (24%) of 54 patients converted to carboplatin subsequently. Thirty (56%) of 54 patients completed all six planned cycles of cisplatin, and 35 (65%) of 54 received all six cycles of platinum. Forty-two (78%) of 54 patients received six cycles of pemetrexed (Supplementary Appendix Table 1). Twenty-seven (50%) of 54 patients received 12 or more durvalumab doses (range 1–18). The median dose intensity (of

cycles received) for cisplatin was 97%, for pemetrexed was 94%, and for durvalumab was 94%. 4 (7%) of 54 participants received a dose reduction in cisplatin, 1 (7%) of 14 received a dose reduction of carboplatin, 6 (11%) of 54 received a dose reduction of pemetrexed, and 4 (7%) of 54 received a dose omission of durvalumab. The median duration on study was 8.1 months (IQR 5.5,12.2). At the time of analysis, all patients have completed study treatment. Patients predominantly discontinued treatment due to disease progression (32 [60%] of 54 patients). Two (4%) of 54 patients discontinued treatment due to treatment-related toxicity, one due to increased creatinine related to durvalumab, and one for cardiac chest pain unrelated to study drug.

Median PFS was 6.9 months by mRECIST (95% CI 5.5–9.0 months, see Figure 1a) and was 7.0 months by iRECIST (95% CI 5.7-9.0 months, see Supplementary Appendix Figure 1). The confirmed RR according to mRECIST was 48% (95% CI 35–61%) with PR in 26 (48%), SD in 21 (37%), and PD in 7 (13%) of 54 participants (Table 2 and Figure 2A). The best confirmed response according to iRECIST was PR in 26 (48%), SD in 22 (41%), and PD in 6 (11%) of 54 participants. There were no complete responses.

An additional 2 (4%) of 54 participants had pseudoprogression with an initial increase in their tumour measurements (one meeting criteria for progression according to mRECIST) before subsequent tumour shrinkage meeting criteria for a PR according to iRECIST (Figure 2B, spider plot). As progression was the first response recorded, these participants were counted as having progressed at 6 months despite their subsequent tumour shrinkage. Among responders, the median time from first response to progression or death was 5.6 months (95% CI 4.9–12.3) (Supplementary Appendix Figure 2, swimmer plot).

Responses were observed in all histologic subtypes, including biphasic and desmoplastic. Of six participants with biphasic disease, one (17%) of 6 had a PR, three (50%) of six SD, and two (33%) of six PD as their best iRECIST response. Of two patients with desmoplastic disease, one had a PR and one SD. One patient with sarcomatoid disease had SD as their best response.

The median follow-up for overall survival of all patients was 28.2 months (IQR 26.5-30.2 months). The median OS was 18.4 months (95% CI 13.1–24.8), with a 12-month survival rate of 64.8% and a 24-month survival rate of 37.0% (Figure 1b). There were five deaths during study treatment. One death, without evidence of radiological progression, was attributed to mesothelioma at autopsy without evidence of any other cause, including no evidence of immunological complications. The four other deaths during study treatment included one with

acute dyspnoea followed by respiratory arrest; one fatal myocardial infarction; one cardiac arrest in the context of pulmonary embolism; and one from aspiration pneumonia complicating recurrent laryngeal nerve palsy due to mesothelioma. None of these deaths were attributed to durvalumab.

The most frequently observed AEs of any grade were fatigue, nausea, peripheral neuropathy, constipation, neutropenia, tinnitus/ hearing impairment, rash, and peripheral oedema (Table 3). A total of 60 serious adverse events (SAEs) occurred within 29 patients; most were attributed to MPM or chemotherapy. Five SAEs were considered possibly related to durvalumab (two renal impairment, one adrenal insufficiency, one infusion reaction, and one visual blurring). Twelve participants experienced irAEs, including five (9%) of 54 with hypothyroidism, two (4%) of 54 with increased amylase/lipase, two (4%) of 54 with pneumonitis, one (2%) of 54 with adrenal insufficiency, one (2%) of 54 with hyperthyroidism, and one (2%) of 54 with renal impairment. AEs resulting in treatment discontinuation occurred in two (4%) of 54 participants. Eight (15%) of 54 participants had irAE of Grade 3 or 4, and seven (13%) of 54 were treated with high-dose steroids or other immunosuppressive drugs. There were no irAEs leading to death.

Tumour tissue was available from 51 (94%) of 54 participants. PD-L1 expression was evident (TPS ≥1%) in 27 (53%) of 51 participants, and not evident (TPS <1%) in the remaining 24 (47%). There was no apparent association between tumour expression of PD-L1 and PFS, with a median PFS of 6.3 months (95% CI 5.3–10.4 months) for patients with PD-L1 negative tumours, and 6.6 months (95% CI 5.5–9.0 months) for patients with PD-L1 positive tumours (Figure 3). Exploratory analyses showed no apparent associations between PFS and PD-L1 expression categorised by a range of cut points for either TPS or CCP (Supplementary Appendix Figures 3-5).

Discussion

To our knowledge, this is the first reported trial testing the combination of an ICI with chemotherapy in advanced mesothelioma. The study met its criterion for activity, with 31 (57.4%) of 54 participants alive and progression free at 6 months, supporting the hypothesis of additional benefit beyond chemotherapy alone. PRs were observed, with 21 (39%) of 54 patients achieving more than 50% reduction in tumour measurements. While many responses were maintained on single-agent durvalumab, when durvalumab was stopped after completing 12 months of treatment most patients treated to that point then experienced progression.

Pseudoprogression was documented in two participants with tumour measurements that first increased then decreased; this was unexpected in the context of combined treatment with an ICI and chemotherapy.[24] However in keeping with our pre-specified analysis plan based on mRECIST, these patients were counted as having progressed for our primary analysis of PFS6 analysis. The potential for pseudoprogression should be considered in future clinical trials, with an allowance for treatment to continue beyond early progression if showing symptom improvement. A previous single-arm, phase Ib trial of cisplatin, pemetrexed and CP-870,893 (a CD40-activating antibody), in 15 previously-untreated participants, PRs were reported in six (40%) of 15, with a median PFS of 6.3 months and median OS of 16.5 months.[25] The RR was comparable to that of cisplatin and pemetrexed alone.

The role of ICI in mesothelioma is still being elucidated. Clinical trials and real-world data have predominantly included participants being treated after one or more lines of chemotherapy.[5-12,26] Single-arm trials of single-agent ICI have demonstrated activity, with RR ranging from 9.4%-24% and median PFS ranging from 2.6-6.2 months. However, a more recent randomised trial did not show a benefit in PFS or OS with pembrolizumab alone versus single agent chemotherapy as second line treatment.[27] For combinations ICI in the second-line setting, reported RR have ranged from 28-29%, with median PFS of approximately 6 months, and OS of approximately 16 months.[10-12] One small, non-comparative study of nivolumab with or without ipilimumab reported differences of 1.6-months in median PFS, four months difference in OS, and 9% in partial response rates, all favouring the combination.[11] Comparisons of outcomes from treatment in the first-line setting versus second-line setting are unhelpful. The activity of combination immunotherapy in the first-line setting is being assessed in the BMS-743 trial, comparing cisplatin and pemetrexed versus ipilimumab and nivolumab.

We found no evidence of an association between PD-L1 expression and treatment outcomes in our trial, acknowledging the limited power and exploratory nature of our analyses. These findings are consistent with those from trials of ICI combined with chemotherapy in other cancers.[18,28] A role for biomarkers as predictors of response to ICI in mesothelioma remains unclear. We did not select participants for our trial according to PD-L1 expression, consistent with most other trials in mesothelioma. For trials of ICIs in the second- and subsequent-line settings, it is doubtful that response would be related to PD-L1 expression in an archival biopsy specimen taken prior to first-line therapy. The tumour biopsies collected in our trial were taken prior to any treatment, but most were diagnostic and relatively small. There is limited understanding of the spatial and temporal heterogeneity of PD-L1 expression in mesothelioma.

Indeed, results from the KEYNOTE-028 clinical trial, which selected only patients with tumour PD-L1 expression,[7] showed relatively similar outcomes to other trials of single-agent nivolumab or pembrolizumab without selection according to PD-L1 status.[6,8] The INITIATE study of ipilimumab and nivolumab as second-line therapy for mesothelioma reported a post hoc analysis of treatment outcomes according to PD-L1 expression status.[10] In that study, tumour biopsies from 34 evaluable patients taken immediately prior to treatment were scored for percentage PD-L1 expression in tumour and immune cells (using the 22C3 antibody) and PD-L1 positivity in either tumour or immune cells was associated with outcomes. We specified cut points for our analyses of PD-L1 expression *a priori*, similar to those in the INITIATE trial. Further studies are needed to determine and validate proposed cut points for PD-L1 expression in mesothelioma. Additional hypothesis-generating translational studies are underway and will be reported separately; these results may further inform translational correlative analyses in our planned randomised phase 3 trial.

The profile of AEs in DREAM was consistent with that expected when combining cisplatin and pemetrexed with durvalumab, drugs with non-overlapping toxicities that allowed chemotherapy to be administered at its standard dose intensity. The five deaths during study treatment were attributed to mesothelioma (1) or other causes, including chemotherapy (4), and none were attributed to durvalumab. In the DETERMINE trial, 6% of participants in the placebo group died during study treatment, of causes similar to those seen in our trial (myocardial infarction, respiratory failure, and lung infection).[5] The rate of death during study treatment was higher than expected, but consistent with the stage of disease, age, and associated comorbidities of our study population.

The main limitation of this study is its single-arm non-comparative design, deliberately chosen to determine if there was sufficient activity to warrant further research in a definitive randomised phase 3 trial. We included few participants with sarcomatoid, desmoplastic, or biphasic tumours, so we were unable to determine if activity differs in these subtypes. Evidence from other studies suggests that PD-L1 expression may be higher in non-epithelioid variants of mesothelioma.[29] We did not collect detailed TNM staging information was not collected incorporating surgical definitions of disease extent.

Our study regimen did not include bevacizumab, a component of the regimen demonstrating the longest OS in randomised trials of treatments for mesothelioma,[3] because it was designed before the results of the MAPS trial were available. Bevacizumab is not approved for this

indication by the USA FDA, nor is it subsidised by the Pharmaceutical Benefits Scheme in Australia. Comparisons of outcomes from our trial versus the MAPS trial are unreliable because of differences in populations, health care settings, and the play of chance. Nevertheless, the results of the MAPS trial highlight possible roles for VEGF blockade in combination with first-line treatment, and in the maintenance setting, underscoring the potential for testing chemotherapy in combination with both immune checkpoint blockade and VEGF blockade.

Results from a similarly-designed clinical trial lead by PrECOG in the USA (PrE0505), are eagerly awaited for independent validation of our findings (NCT02899195). As progression was frequently observed soon after stopping durvalumab at 12 months, it may be appropriate to continue immunotherapy beyond 12 months, until progression or toxicity, in future clinical trials. It may also be advisable to allow continuation of therapy beyond early progression given our observation of two participants with pseudoprogression. An update of the modified RECIST 1.1 for mesothelioma incorporates guidance for response assessment in immunotherapy trials.[30]

In conclusion, the DREAM trial met its criteria for activity and safety worthy of further research in a proposed randomised phase 3 trial, with outcomes from chemo-immunotherapy that accord with emerging evidence of the efficacy of this strategy in other thoracic cancers.

Author contributions

AKN, WJL, MS, SY and CB contributed to the study design. PSK, BGMH, KJO, DJK, SCHK, CL, AC, TJ, CK, NP, KB, WSL, and AL collected, analysed and interpreted the data. All authors drafted the manuscript and approved the final draft.

Data sharing statement

There are no plans to make participant data or related documentation available.

Declaration of interests

AKN reports grants from AstraZeneca, grants and other from Douglas Pharmaceuticals, and other from Bayer Pharmaceuticals, Roche Pharmaceuticals, Boehringer Ingelheim, Merck Sharp Dohme, Pharmabcine, Atara Biotherapeutics, and Trizell Ltd, during the conduct of the study. WJL reports grants from AstraZeneca during the conduct of the study; grants and personal fees from Douglas Pharmaceuticals, personal fees from MSD, grants from ENA Therapeutics, outside the submitted work; in addition, WJL has patents WO2016015095 and PCT/AU2018/900962 pending. BGMH reports other from AstraZeneca, Roche, Pfizer, BMS and MSD outside the submitted work. TJ reports personal fees from Pfizer, AstraZeneca, BMS, Merck, MSD, Takeda, Boehringer ingelheim, Roche, Ignyta, Novartis, and Bayer, outside the submitted work. SC-HK reports grants and personal fees from AstraZeneca during the conduct of the study; personal fees from MSD, Roche, Pfizer, Boeringher Ingelheim, and BMS, outside the submitted work. NP reports grants and personal fees from Pfizer, personal fees from AstraZeneca, BMS, Merck KgA, MSD, Takeda, Boehringer Ingelheim, Roche, Novartis, grants and Bayer, outside the submitted work. Dr O'Byrne has received advisory board and/or speaker bureau and/or meeting travel/registration support from BMS, MSD, LillyOncology, Boehringer-Ingelheim, Pfizer, Novartis, Roche-Genentech, Teva, Mundipharma, Astrazeneca, Janssen and Natera. He is a stockholder on two startup companies, CARP and CARPE VITAE Pharmaceuticals. Dr. Karapetis reports personal fees from MSD, Astra Zeneca, BMS, and Roche during the conduct of the study. SY reports grants and non-financial support from AstraZeneca during the conduct of the study and grants and non-financial support from AstraZeneca outside the submitted work. MRS reports grants from Astellas, Amgen, AstraZeneca, Bayer, Bionomics, Bristol-Myers Squibb, Celgene, Medivation, Merck Sharp & Dohme, Pfizer, Roche, Sanofi, and Tilray outside the submitted work. P-SK, CB, DJK, CL, AMC, KB, W-SL and AL declare no conflicts of interest.

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Table Legends

Figure Legends

Supplementary Appendix