# Tremelimumab as second-line or third-line treatment in relapsed malignant mesothelioma (DETERMINE): a multicentre, international, randomised, double-blind, placebo-controlled phase 2b trial

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## Summary

**Background** New therapeutic strategies for malignant mesothelioma are urgently needed. In the DETERMINE study, we investigated the effects of the cytotoxic-T-lymphocyte-associated antigen 4 (CTLA-4) monoclonal antibody tremelimumab in patients with previously treated advanced malignant mesothelioma.

**Methods** DETERMINE was a double-blind, placebo-controlled, phase 2b trial done at 105 study centres across 19 countries in patients with unresectable pleural or peritoneal malignant mesothelioma who had progressed after one or two previous systemic treatments for advanced disease. Eligible patients were aged 18 years or older with Eastern Cooperative Oncology Group performance status of 0 or 1 and measurable disease as defined in the modified Response Evaluation Criteria In Solid Tumors (RECIST) version 1.0 for pleural mesothelioma or RECIST version 1.1 for peritoneal mesothelioma. Patients were randomly assigned (2:1) in blocks of three, stratified by European Organisation for Research and Treatment of Cancer status (low risk *vs* high risk), line of therapy (second line *vs* third line), and anatomic site (pleural *vs* peritoneal), by use of an interactive voice or web system, to receive intravenous tremelimumab (10 mg/kg) or placebo every 4 weeks for 7 doses and every 12 weeks thereafter until a treatment discontinuation criterion was met. The primary endpoint was overall survival in the intention-to-treat population. Safety was assessed in all patients who received at least one dose of study drug. The trial is ongoing but no longer recruiting participants, and is registered with ClinicalTrials.gov, number NCT01843374.

**Findings** Between May 17, 2013, and Dec 4, 2014, 571 patients were randomly assigned to receive tremelimumab (n=382) or placebo (n=189), of whom 569 patients received treatment (two patients in the tremelimumab group were excluded from the safety population because they did not receive treatment). At the data cutoff date (Jan 24, 2016), 307 (80%) of 382 patients had died in the tremelimumab group and 154 (81%) of 189 patients had died in the placebo group. Median overall survival in the intention-to-treat population did not differ between the treatment groups: 7·7 months (95% CI 6·8–8·9) in the tremelimumab group and 7·3 months (5·9–8·7) in the placebo group (hazard ratio 0·92 [95% CI 0·76–1·12], p=0·41). Treatment-emergent adverse events of grade 3 or worse occurred in 246 (65%) of 380 patients in the tremelimumab group and 91 (48%) of 189 patients in the placebo group; the most common were dyspnoea (34 [9%] patients in the tremelimumab group *vs* 27 [14%] patients in the placebo group), diarrhoea (58 [15%] *vs* one [<1%]), and colitis (26 [7%] *vs* none). The most common serious adverse events were diarrhoea (69 [18%] patients in the tremelimumab group *vs* one [<1%] patient in the placebo group), dyspnoea (29 [8%] *vs* 24 [13%]), and colitis (24 [6%] *vs* none). Treatment-emergent events leading to death occurred in 36 (9%) of 380 patients in the tremelimumab group and 12 (6%) of 189 in the placebo group; those leading to the death of more than one patient were mesothelioma (three [1%] patients in the tremelimumab group *vs* two [1%] in the placebo group), dyspnoea (three [1%] *vs* two [1%]); respiratory failure (one [<1%] *vs* three [2%]), myocardial infarction (three [1%] *vs* none), lung infection (three [1%] patients *vs* none), cardiac failure (one [<1%] *vs* one [<1%]), and colitis (two [<1%] *vs* none). Treatment-related adverse events leading to death occurred in five (1%) patients in the tremelimumab group and none in the placebo group. The causes of death were lung infection in one patient, intestinal perforation and small intestinal obstruction in one patient; colitis in two patients, and neuritis and skin ulcer in one patient.

**Interpretation** Tremelimumab did not significantly prolong overall survival compared with placebo in patients with previously treated malignant mesothelioma. The safety profile of tremelimumab was consistent with the known safety profile of CTLA-4 inhibitors. Investigations into whether immunotherapy combination regimens can provide greater efficacy than monotherapies in malignant mesothelioma are ongoing.

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## Research in context

### Evidence before this study

We searched PubMed for reports published in English from Jan 1, 2006, to Dec 31, 2016, using the terms "mesothelioma", "anti-CTLA-4", and "immunotherapy", and limited our results to clinical trials. There are currently no approved second-line therapies for patients with relapsed or refractory malignant mesothelioma; thus, new treatments are urgently needed. Therapeutic blockade of the immune checkpoint cytotoxic-T-lymphocyte-associated antigen 4 (CTLA-4) has been shown to result in durable clinical benefit in melanoma and thus could be efficacious for other indications, including mesothelioma. In a preliminary study of tremelimumab (15 mg/kg every 90 days) in malignant mesothelioma, early evidence of clinical activity was recorded. However, retrospective data from studies of melanoma suggested that this dosing schedule might have resulted in tremelimumab underexposure. As such, an intensified dosing schedule of tremelimumab (10 mg/kg every 4 weeks for seven doses followed by the same dose every 12 weeks thereafter) was then investigated and showed promising antitumour activity and an acceptable safety profile in mesothelioma. These data led to the assessment of tremelimumab in patients with malignant mesothelioma in a randomised setting in this phase 2b trial.

### Added value of this study

This Article is the first publication on DETERMINE, a randomised clinical trial investigating the antitumour activity and safety of tremelimumab versus placebo in patients with previously treated malignant mesothelioma. In this study, tremelimumab did not significantly prolong overall survival compared with placebo. No clinically meaningful differences in progression-free survival or the proportion of patients achieving objective responses were recorded between the treatment groups. The safety data were consistent with those reported previously for tremelimumab, as well as with other CTLA-4 inhibitors in other tumour types.

### Implications of all the available evidence

Our results provide further information about the clinical utility of anti-CTLA agents in malignant mesothelioma and show that patients with malignant mesothelioma do not derive clinical benefit from single-agent tremelimumab. Preliminary studies investigating other checkpoint inhibitors (eg, anti-PD-1/PD-L1) have shown early signs of clinical activity with an acceptable safety profile. Ongoing studies are investigating whether combinations of anti-CTLA-4 and anti-PD-1/PD-L1 agents will be efficacious in patients with malignant mesothelioma.

## Introduction

Malignant mesothelioma is an asbestos-related tumour that mainly originates in the pleural and peritoneal mesothelial surfaces.[1] Most cases are pleural malignant mesothelioma, with a smaller proportion of patients presenting with primary peritoneal disease.[2] Cisplatin and pemetrexed combination therapy is the recommended first-line treatment for advanced pleural malignant mesothelioma.[3] Although no first-line treatments have been approved for advanced peritoneal disease, cisplatin and pemetrexed are also commonly used in this population.[3] The addition of bevacizumab to cisplatin and pemetrexed combination therapy has been shown to significantly improve overall survival compared with cisplatin and pemetrexed alone in newly diagnosed pleural malignant mesothelioma.[4] No therapies have shown survival benefit as second-line treatments for relapsed or refractory disease and consequently no agents have been approved for use following progression on first-line therapy.

Immunotherapy-based immune checkpoint blockade has shown promising antitumour activity across various types of cancer.[5] Malignant mesothelioma is associated with lymphocyte infiltration,[6] including regulatory T cells and inhibitory cytokines that induce a highly immunosuppressive environment within the tumour.[7] Thus, a rationale exists for investigating immunotherapy-based regimens in advanced malignant mesothelioma.

Cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) is a co-inhibitory receptor expressed on T cells that reduces the amplitude of CD28-mediated T-cell activation by competitively binding to CD80 (B7-1) and CD86 (B7-2) ligands.[8] Blockade of CTLA-4 enhances T-cell activation and might be associated with antitumour immune responses. The CTLA-4 inhibitor ipilimumab has been shown to lead to a durable survival benefit in patients with metastatic melanoma.[9]

Tremelimumab is a selective human immunoglobulin G2 monoclonal antibody against CTLA-4[10] that promotes T-cell activity but does not deplete regulatory T cells.[11] Tremelimumab showed clinical activity in two investigator-initiated phase 2, open-label, single-arm, single-centre studies, each of which enrolled 29 patients with chemotherapy-resistant advanced malignant mesothelioma.[12,13] In the first trial (MESOT-TREM-2008),[12] tremelimumab was given at a dose of 15 mg/kg every 90 days; median progression-free survival was 6·2 months (95% CI 1·3–11·1) and median overall survival was 10·7 months (0·0–21·9). However, a retrospective analysis of data from patients with melanoma suggested that this dose might have led to underexposure to tremelimumab[14] and therefore the second trial (MESOT-TREM-2012)[13] used an intensified dosing schedule (10 mg/kg given every 4 weeks for six doses, then every 12 weeks). The clinical activity of tremelimumab was encouraging, with four (14%) immune-related partial responses, immune-related progression-free survival of 6·2 months (95% CI 5·7–6·7), median overall survival of 11·3 months (3·4–19·2), and 1 year survival of 48·3% (30·1–66·5).[13] Tremelimumab also had a manageable tolerability

profile,[13] consistent with that reported in other tumour types.[15] These data led to further assessment of tremelimumab in a randomised setting in patients with advanced malignant mesothelioma.

In this Article, we present results from the DETERMINE trial, which compared tremelimumab with placebo in patients with unresectable pleural or peritoneal malignant mesothelioma after progression on one or two previous systemic treatments for advanced disease.

## Methods

### Study design and participants

DETERMINE was an international, multicentre, randomised, double-blind, placebo-controlled, phase 2b trial done at 105 study centres in 19 countries (appendix pp 19–22). Eligible patients were aged 18 years or older with histologically or cytologically confirmed unresectable pleural or peritoneal malignant mesothelioma that had progressed after one or two previous systemic treatments for advanced disease, as confirmed by investigators (who also confirmed the stage of disease). Progression at inclusion was investigator-determined based on standard clinical criteria such as evidence of radiological or clinical progression. Previous systemic treatment must have included a first-line pemetrexed (or other anti-folate)-based regimen in combination with a platinum agent; for patients in whom pemetrexed was contraindicated, not tolerated, or not an approved therapy (eg, those with peritoneal mesothelioma), previous treatment with a first-line platinum-based regimen was required. Additionally, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and measurable disease, defined as at least one measurable lesion that could be accurately assessed at baseline by CT or MRI and suitable for repeated measurements (in accordance with modified Response Evaluation Criteria In Solid Tumors [RECIST] version 1.0 for pleural mesothelioma[16] or RECIST version 1.1 for peritoneal mesothelioma[17]), were also required for enrolment. Patients with any histological subtypes of malignant mesothelioma (epithelioid, sarcomatoid, and biphasic) were allowed to participate. Eligible patients had to have adequate bone marrow, hepatic, and renal function measured within 14 days before randomisation, which were defined as platelet count of at least 75 000 platelets per mL, an absolute neutrophil count of at least 1000 cells per mL, haemoglobin of at least 9 g/dL, total bilirubin up to 1·5-times the upper limit of normal (ULN; except for patients with Gilbert's syndrome [>5 times ULN] or those with liver metastasis, who had to have baseline total bilirubin ≤3·0 mg/dL); aspartate aminotransferase and alanine aminotransferase up to three times the ULN (≤5 times ULN for patients with liver metastasis); and serum creatinine up to 2·0 mg/dL or calculated creatinine clearance of at least 50 mL/min as calculated with the Cockcroft-Gault equation. Negative screening test results for HIV and hepatitis A, B, and C were also required for eligibility.

Patients were excluded if they had failed more than two previous systemic treatments for advanced malignant mesothelioma, or had received any previous monoclonal antibody against CTLA-4, programmed cell death 1 (PD-1), or programmed cell death ligand 1 (PD-L1). Patients who received chemotherapy or radiotherapy less than 2 weeks before randomisation and those who were receiving systemic corticosteroids or other immunosuppressive medications, or with a condition that necessitated chronic use of corticosteroids, were also excluded.

Patients were not eligible for the study if they had a history of chronic inflammatory or autoimmune disease with symptomatic disease within 3 years before randomisation; active, untreated CNS metastasis; history of other malignancy unless the patient had been disease-free for at least 3 years; active or history of diverticulitis, inflammatory bowel disease, irritable bowel syndrome, coeliac disease or other serious gastrointestinal chronic conditions associated with diarrhoea; active or history of systemic lupus erythematosis or Wegener's granulomatosis; or a history of sarcoidosis syndrome. Additional inclusion and exclusion criteria are described in the appendix (p 2).

See Online for appendix

The study was done in accordance with the ethical principles of the Declaration of Helsinki and the International Council on Harmonization guidelines on Good Clinical Practice. The study protocol was reviewed and approved by the Institutional Review Board or independent ethics committee at all participating centres. The full trial protocol is available online.

For the **trial protocol** see https://astrazenecagrouptrials.pharmacm.com/ST/Submission/View?id=13

All patients provided written informed consent to participate.

### Randomisation and masking

By use of an interactive voice or web response system, patients were randomly assigned (2:1) to treatment with tremelimumab or matching placebo. Randomisation was stratified by European Organisation for Research and Treatment of Cancer (EORTC) status (low risk *vs* high risk),[18] line of therapy (second line *vs* third line), and anatomic site (pleural *vs* peritoneal). Enrolment of patients without previous first-line pemetrexed-based treatment was capped at 20%. Treatment was allocated in blocks of three via a schedule generated by Perceptive Informatics (Nottingham, UK) who used a computerised randomised list generator. Patients, treating physicians, and representatives of the study funder were masked to study treatment assignment. The interactive voice or web response system was used to assign the investigational product kit numbers to patients, and tremelimumab and placebo were identically labelled and indistinguishable in appearance.

### Procedures

Patients received tremelimumab (intravenous infusion at 10 mg/kg) or matching placebo, every 4 weeks for seven doses as induction treatment, followed by

maintenance dosing every 12 weeks until a treatment discontinuation criterion was met. Permanent discontinuation criteria included withdrawal of patient consent, loss to follow-up, pregnancy or intent to become pregnant, patient non-compliance, initiation of alternative anticancer therapy, confirmed disease progression, adverse event or laboratory abnormality contraindicating further dosing or two consecutive doses missed due to ongoing treatment-related adverse event (appendix p 2), and administration of infliximab or another tumour necrosis factor α inhibitor. No dose reductions were allowed. Criteria for skipping the next scheduled dose included ongoing grade 2 treatment-related laboratory abnormalities or toxicities (appendix p 2), as assessed with National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE). Persistent CTCAE grade 1 treatment-related toxicities (duration >10 days) were managed in the same way as CTCAE grade 2 toxicities. All treatment-related toxicities had to be resolved to grade 1 or lower before dosing could be resumed at the next scheduled dose.

Clinical laboratory assessments included serum chemistry, haematology, and urinalysis and were done at baseline, every 4 weeks during the induction period, every 6 weeks during weeks 25–61, and every 3 months thereafter, and at the end of treatment and every 30 days through to 90 days after the last dose. Adverse events were recorded continuously from the first dose to 90 days after the last dose of tremelimumab or placebo, graded in accordance with CTCAE version 3.0.

Tumour imaging assessments were done at baseline and every 3 months during the induction dosing period, every 6 weeks during weeks 25–61, and every 3 months thereafter, until confirmed objective disease progression, irrespective of whether or not the patient discontinued study drug. A modified version of RECIST for mesothelioma[16] was used to assess pleural mesothelioma via CT scans of the chest, abdomen, and pelvis, and peritoneal mesothelioma was assessed with RECIST v1.1.[17]

Given that an initial increase in tumour burden or the appearance of new lesions could precede immunotherapy-induced tumour regression,[19] patients initially assessed as having progressive disease on RECIST criteria for mesothelioma, in the absence of significant clinical deterioration warranting discontinuation of study treatment, were to continue treatment and receive a confirmatory scan at least 4 weeks later.[19] If the tumour burden at the confirmatory scan was more than 20% larger than the tumour burden at the initial scan showing progressive disease, the patient was deemed to have confirmed progressive disease and was to be discontinued from study treatment. However, if the tumour burden at the confirmatory scan was within 20% of the tumour burden at the initial scan showing progressive disease, the patient was deemed to have stable disease and was to continue treatment until the next scheduled scan 3 months after the initial progressive disease. Any subsequent scheduled tumour assessment visit showing that the tumour burden was more than 20% larger than the tumour burden at the initial scan showing progressive disease was regarded as confirmed progressive disease, and the patient was to be discontinued from study treatment.

Patient-reported outcomes were assessed with the Lung Cancer Symptom Scale-mesothelioma (LCSS-Meso; for disease-related symptoms and health-related quality of life), Brief Pain Inventory-Short Form (BPI-sf; for pain), and EQ-5D 3 level version (EQ-5D-3L; for health status), and collected with an electronic patient-reported outcome device. The BPI-sf questionnaire was collected before any study procedures at screening, at or before study visits during the induction and maintenance treatment periods, and at the end of treatment. An exception to this was for the BPI-sf worst pain score item, which was collected daily. The LCSS-Meso questionnaire was collected at screening, daily during the induction and maintenance treatment periods, and at the end of treatment. Other assessments included pharmacokinetics and anti-tremelimumab antibodies, which were measured with a validated electrochemiluminescence assay on a Meso Scale Discovery platform (Meso Scale Diagnostics, Rockville, MD, USA).

All patients were followed up for safety at 30, 60, and 90 days (or within 3 days of each timepoint) after the last dose of tremelimumab or placebo or at the time of initiation of new systemic anticancer treatment. After 90 days, only patients with treatment-related serious adverse events were followed up for safety. All patients were followed up for survival every 3 months (or within 14 days of each timepoint) until the end of the study.

### Outcomes

The primary endpoint was overall survival, which was defined as the time from randomisation until death from any cause. For patients who were alive at the time of data cutoff for the primary analysis or lost to follow-up, overall survival was censored on the last date when patients were known to be alive.

Secondary endpoints were 18-month overall survival (proportion of patients alive at 18 months, as estimated with the Kaplan-Meier method), disease control (proportion of patients with a best response of complete response, partial response, or stable disease for at least 12 weeks' duration measured from date of randomisation; this endpoint was prospectively added as an additional variable to the statistical analysis protocol before the database lock and unblinding of the study) and durable disease control (proportion of patients with best response of complete response, partial response, or stable disease for at least 6 months measured from the date of randomisation), progression-free survival (time from randomisation to the first record of disease progression or death from any cause [whichever occurred first], censored at the last tumour assessment

date for patients who were alive and progression-free at the time of data cutoff), proportion of patients achieving an objective response (complete response or partial response), duration of response (time from first documentation of objective response [complete response or partial response] to the first documented disease progression or death from any cause, whichever occurred first), patient-reported outcomes, pharmacokinetics (not reported in this Article), immunogenicity of tremelimumab, and safety and tolerability. The two key patient-reported outcome endpoints were time to deterioration in worst pain (from BPI-sf) and time to deterioration of disease-related symptoms (using the symptom burden index [SBI] from LCSS-Meso). The evaluation of these endpoints is described in detail in the appendix (p 2).

Safety endpoints included adverse events and serious adverse events, changes from baseline in clinical laboratory assessments, electrocardiogram results, and vital signs. To aid detection of important toxicities or reactions that are associated with the anti-CTLA-4 drug class (ie, ipilimumab), we analysed the following categories of adverse events of special interest: diarrhoea; colitis or enterocolitis; endocrinopathy; dermatitis; hepatitis or hepatic toxicity; hypersensitivity reactions, anaphylaxis, or infusion reactions; pneumonitis or interstitial lung disease; neuropathy or neuromuscular toxic effects; pancreatitis; and renal failure or nephritis (appendix pp 2–3).

Exploratory objectives were: to estimate and compare durable disease control, progression-free survival, proportion of patients achieving an objective response, and duration of response based on immune-related response criteria between the two treatment arms; to examine health-related quality of life, disease-related symptoms, pain, and health status in patients with durable clinical activity; and to examine biomarkers and their association with tremelimumab treatment and clinical outcome. The results of these analyses are not reported in this Article.

### Statistical analysis

The formal statistical analysis for this trial was to test the following hypotheses: H0, that there was no difference between tremelimumab and placebo; and H1, that there was a difference between tremelimumab and placebo. The trial was amended from a 180-patient phase 2 trial (80% power with a two-sided α of 0·20) because of a review of data from two single-arm, investigator-initiated phase 2 studies in mesothelioma.[12,13] At the time of this protocol amendment (Jan 23, 2014), neither the funder nor the investigators were aware of treatment allocation within the study because of the double-blind design. The study had randomised 107 patients prior to this amendment and written approval was obtained from the appropriate Institutional Review Board or Independent Ethics Committee before the implementation of the amendment. After the amendment, the planned sample size of the study was changed to about 564 patients (randomised 2:1), on the basis of a group sequential design with two planned interim analyses. The sample size and power calculations were based on simulations under a nonproportional hazard model that accounted for the potential delayed treatment effect for immunotherapy. Assuming an exponential distribution of overall survival with a median time of 7 months for placebo and a 4-month delayed effect (ie, hazard ratio [HR] of 1 for the first 4 months and HR of 0·56 thereafter) for tremelimumab, 456 overall survival events (deaths) were needed to provide approximately 90% power and to control the overall two-sided α of 0·05 with two planned interim analyses. Under these assumptions, the 1000 simulations generated a mean overall HR of 0·71 and a median overall survival of 7·0 months for the placebo group and 9·3 months for the tremelimumab group.

The primary endpoint of overall survival was compared between the two treatment groups in the intention-to-treat population (all randomised patients) via a stratified log-rank test. We estimated the HR of tremelimumab versus placebo and the 95% CI with a stratified Cox regression model. The planned stratification factors were anatomic site, EORTC status, and line of therapy. However, because of the low percentage of randomised patients with peritoneal malignant mesothelioma (<5%), only the stratification variables of EORTC status and line of therapy were included within the final stratified statistical analysis, as prespecified in the statistical analysis plan, before unblinding and database lock. A hierarchical gate-keeping strategy was applied in this study, in which hypotheses were tested in a predefined order, where overall survival (primary endpoint) was tested first. The other hypotheses were then tested in the multiple testing procedure with an α-exhaustive recycling strategy.[20] We used the intention-to-treat population for the primary analysis of all secondary efficacy endpoints. We compared overall survival at 18 months, estimated with the Kaplan-Meier method, between the two treatment groups via a normal approximation under a complementary log-log transformation,[21] stratified by EORTC status and line of therapy. We analysed progression-free survival (based on investigator-determined response data) with the same methods as for the primary endpoint. We estimated 95% CIs for durable disease control, disease control, and the proportion of patients achieving an objective response for each treatment group using an exact probability method. Sensitivity analyses for overall survival included assessment of the pattern of censoring between the two treatment groups. We generated a Kaplan-Meier plot of time to censoring in which the censoring and event flags were reversed. Additionally, we did subgroup analyses of overall survival (prespecified subgroups were EORTC status [low risk *vs* high risk], line of therapy [second *vs* third] anatomic site [pleural *vs* peritoneal], age [<65 years *vs* ≥65 years], race [white *vs* not white], C-reactive protein

level [≤1·5 *vs* >1·5 times ULN), sex [male *vs* female], histology [epithelioid, sarcomatoid, and biphasic] and country [USA *vs* non-USA]) and a global interaction test at the 0·1 level of significance for the Cox regression model to establish whether there were any potential treatment-by-covariate interactions.

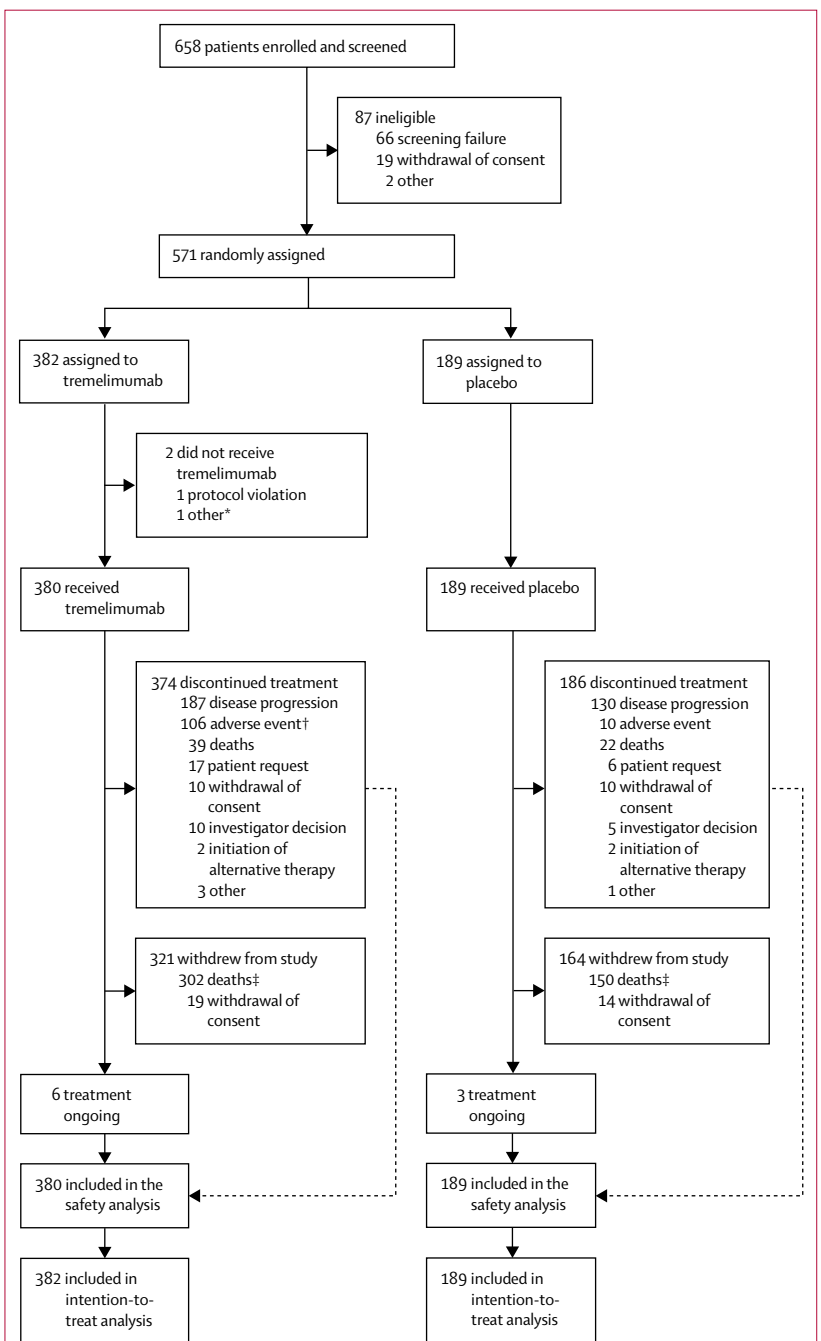


***Figure 1:*** **Trial profile**
*History of diverticulitis discovered after randomisation. †Two of these patients had non-treatment emergent adverse events starting >90 days after the last dose of tremelimumab. ‡Another five patients in the tremelimumab group and four patients in the placebo group died after withdrawal of consent.

We evaluated patient-reported outcomes of time to deterioration in worst pain (from BPI-sf) in the intention-to-treat population subset who reported asymptomatic or minimal pain at baseline and who did not take opioids within 4 weeks before randomisation, and evaluated time to deterioration of disease-related symptoms (SBI from LCSS-Meso) in patients with pleural mesothelioma in the intention-to-treat population. We analysed the patient-reported outcome time to deterioration endpoints using the same methods as for the primary endpoint.

Tolerability and safety were assessed by summarising adverse events and serious adverse events occurring from the first dose of study drug to 90 days after the last dose, electrocardiogram results, ECOG performance status, vital signs, and laboratory assessments (including haematology and blood chemistry) during the study. We based the tolerability and safety analyses on the safety population (all patients who received at least one dose of study drug), with analysis by treatment group and for all patients combined. The safety analysis was descriptive in nature and we made no formal statistical comparisons.

Two interim analyses were planned: the first to assess futility and superiority of overall survival; the second to assess superiority of overall survival only. The first interim analysis was planned to be done after 128 overall survival events (deaths) had occurred in the first 180 patients randomised, with the futility analysis based on these 180 patients and superiority analysis based on all patients randomised up to that time. The second interim analysis was planned to be done after 342 overall survival events had been observed. An independent data monitoring committee of external experts reviewed the data and informed the funder whether the interim boundaries were crossed. The futility boundary at the first interim analysis was based on the predictive power being less than 10% (corresponding roughly to an HR of 1). The interim and final efficacy boundaries were based on O'Brien–Fleming type flexible α-spending methods. The actual efficacy boundaries at the two interim and final analyses were to be adjusted according to the actual number of observed events at each analysis so that the overall type I error was controlled at the two-sided 0·05 level by use of ADDPLAN version 6.0 (appendix p 5).

We did all data analyses with the SAS system version 9.3 in a UNIX environment. This study is registered with ClinicalTrials.gov, number NCT01843374.

## Role of the funding source

The funder provided study drugs, was involved in the study design, data collection, data analysis, data interpretation, and preparation of the report, and gave approval to submit for publication. All authors had full access to the data used to write the report, and the corresponding author had final responsibility for the decision to submit the Article for publication.

| | Tremelimumab (n=382) | Placebo (n=189) |
|---|---|---|
| Age (years) | 66·0 (60·0–72·0) | 67·0 (61·0–73·0) |
| Sex | | |
| Male | 283 (74%) | 151 (80%) |
| Female | 99 (26%) | 38 (20%) |
| Race | | |
| White | 372 (97%) | 183 (97%) |
| Asian | 7 (2%) | 2 (1%) |
| Other | 3 (<1%) | 3 (2%) |
| Missing data | 0 | 1 (<1%) |
| Disease site | | |
| Pleural | 364 (95%) | 181 (96%) |
| Peritoneal | 18 (5%) | 8 (4%) |
| Histology | | |
| Epithelioid | 318 (83%) | 157 (83%) |
| Sarcomatoid | 22 (6%) | 16 (8%) |
| Biphasic or mixed | 40 (10%) | 16 (8%) |
| Missing data | 2 (<1%) | 0 |
| Disease stage* | | |
| I | 0 | 1 (<1%) |
| IB | 1 (<1%) | 3 (2%) |
| II | 14 (4%) | 7 (4%) |
| III | 95 (25%) | 39 (21%) |
| IV | 263 (69%) | 133 (70%) |
| Not available | 3 (1%) | 3 (2%) |
| Unknown | 6 (2%) | 3 (2%) |
| ECOG performance status | | |
| 0 | 106 (28%) | 57 (30%) |
| 1 | 273 (71%) | 132 (70%) |
| Missing data | 3 (<1%) | 0 |
| Number of previous therapies | | |
| 1 | 240 (63%) | 119 (63%) |
| 2 | 142 (37%) | 70 (37%) |
| Received previous first-line pemetrexed-based treatment | | |
| Yes | 377 (99%) | 187 (99%) |
| No | 5 (1%) | 2 (1%) |
| EORTC status | | |
| High risk | 162 (42%) | 79 (42%) |
| Low risk | 220 (58%) | 110 (58%) |

Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group. EORTC=European Organisation for Research and Treatment of Cancer.
*Disease stage assessed via the TNM staging system.

***Table 1:*** **Baseline characteristics**

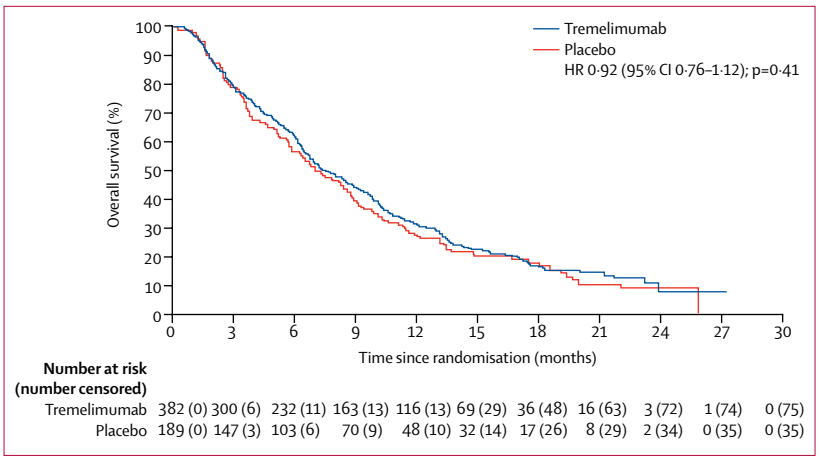


***Figure 2:*** **Overall survival**
EORTC=European Organisation for Research and Treatment of Cancer. HR=hazard ratio.

## Results

Between May 17, 2013, and Dec 4, 2014, 658 patients were enrolled into the DETERMINE study. Trial accrual was very rapid. The independent data monitoring committee recommended the study continue at both interim analyses because futility (first interim analyses only [predictive power <10%]) and superiority boundaries were not met. As such, we present the final analyses of results. At the time of the final analysis data cutoff (Jan 24, 2016), 571 patients had been randomly assigned to tremelimumab (n=382) or placebo (n=189) and were included in the intention-to-treat analysis set and analysed for overall survival (figure 1); 87 patients were not assigned to treatment (ie, were excluded from the intention-to-treat analysis) because of screening failure (n=66), consent withdrawal (n=19), or other reasons (n=2). 569 patients received study treatment, including 380 who received tremelimumab and 189 who received placebo, and were included in the safety analysis set. Patient demographics and baseline characteristics were balanced across the two treatment groups, with most patients being elderly (median age 66·0 years [IQR 60·0–72·0]) and male (434 [76%] of 571 patients). Of the 571 patients randomised, 545 (95%) had pleural malignant mesothelioma, 475 (83%) had epithelioid histology, and 530 (93%) had stage III or IV disease at study entry (table 1). The median number of doses was 3·0 (IQR 2·0–5·0) and median dose intensity was 100% (75·7–100·0) with tremelimumab and 100% (90·3–100·0) with placebo. Median treatment duration was 57·0 days (IQR 29·0–113·5) in the tremelimumab group and 58·0 days (30·0–140·0) in the placebo group. 61 (16%) of the 382 patients assigned to tremelimumab remained on-study (six patients still receiving trial treatment) at data cutoff versus 25 (13%) of 189 patients in the placebo group (three patients still receiving trial treatment). The most common reason for treatment discontinuation was disease progression (187 [49%] of 382 patients in the tremelimumab group and 130 [69%] of 189 patients in the placebo group). Death was the most common reason for study withdrawal (302 [79%] of 382 patients in the tremelimumab group and 150 [79%] of 189 patients in the placebo group).

At data cutoff, 461 patients had died: 307 (80%) of 382 in the tremelimumab group and 154 (82%) of 189 in the placebo group (appendix p 6). Median overall survival did not differ significantly between the treatment groups: it was 7·7 months (95% CI 6·8–8·9) in the tremelimumab

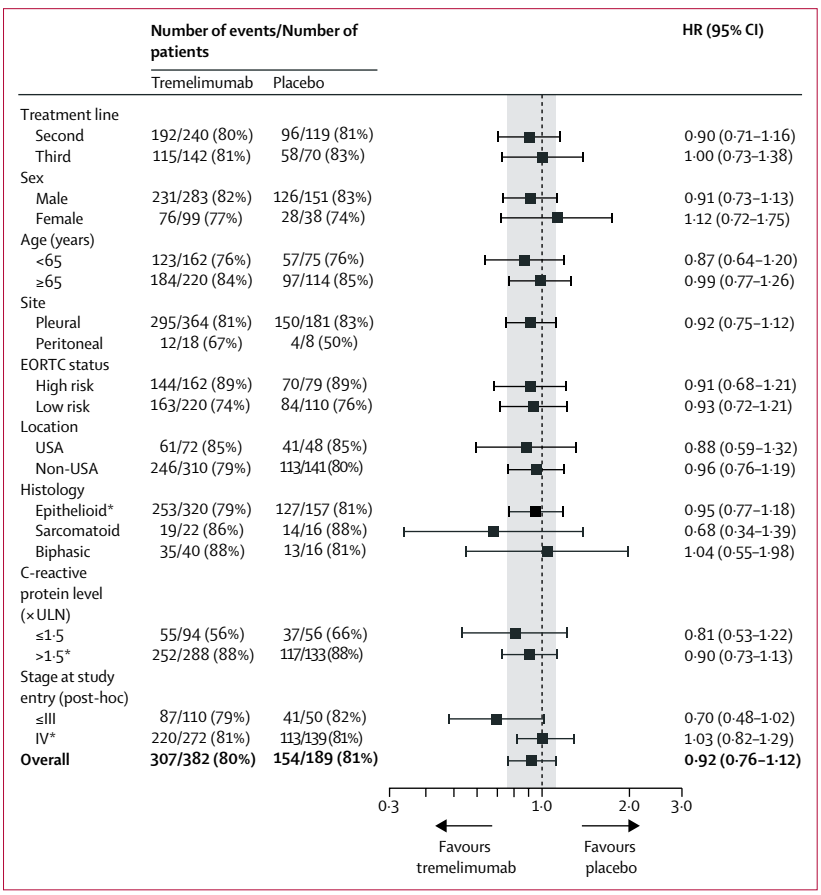


***Figure 3:*** **Subgroup analysis of overall survival**

Overall HR derived from a stratified Cox analysis of overall survival in the intention-to-treat population, stratified by EORTC status and line of therapy; subgroups were derived from unadjusted Cox analysis. Shading represents the size of 95% CI for the overall intention-to-treat population. HRs are not presented if there were fewer than ten events in a subgroup in either treatment group. *Includes missing values. HR=hazard ratio. EORTC=European Organisation for Research and Treatment of Cancer. ULN=upper limit of normal.

group and 7·3 months (5·9–8·7) in the placebo group (HR 0·92, 95% CI 0·76–1·12, p=0·41; figure 2). A plot of the complementary log-log of the estimated survivor function versus log(time) by treatment group showed little evidence of non-proportional hazards, since lines on the plot were reasonably parallel and crossover was not extensive (appendix p 17). Additionally, formal testing with a model including terms for treatment and a treatment time-dependent variable of the proportionality assumption, as well as the stratification factors of EORTC status and line of therapy, provided a p value of 0·996.

Overall survival was generally consistent across prespecified subgroups, including treatment line, sex, age, and EORTC status, as well as exploratory post-hoc subgroups (disease stage at study entry; figure 3). The global interaction test for the two stratification factors (EORTC status and line of therapy) was not significant at the 10% level (p=0·97).

Because a hierarchical gate-keeping strategy was applied and the primary endpoint was not met, statistical significance could not be assessed for the other endpoints. However, point estimates, CIs and p values are presented for information. Overall survival at 18 months did not differ between treatment groups (17·4% [95% CI 13·4–21·8] in the tremelimumab group and 18·2% [12·7–24·5] in the placebo group; HR 1·01 [95% CI 0·79–1·29], p=0·926). We detected no clinically meaningful differences in progression-free survival between tremelimumab and placebo (appendix p 18). Objective responses were achieved by 17 (4·5%, 95% CI 2·6–7·0) of 382 patients receiving tremelimumab (table 2), all of which were partial responses. In the placebo group, two (1·1%, 0·1–3·8) of 189 patients achieved an objective response, both of which were also partial responses. The median duration of response was 4·8 months (95% CI 2·6–8·3) in the tremelimumab group and 5·6 months (2·8–8·3) in the placebo group. In the tremelimumab group, 106 (27·7%, 23·3–32·5) of 382 patients achieved disease control, compared with 41 (21·7%, 16·0–28·3) of 189 patients in the placebo group. 64 (16·8%, 95% CI 13·1–20·9) of 389 patients in the tremelimumab group and 22 (11·6%, 7·4–17·1) of 189 patients in the placebo group had durable disease control. Patient-reported outcome analyses are described in the appendix (p 4), but interpretation of patient-reported outcome data was limited by the absence of data collection beyond the end of treatment or discontinuation. The incidence of anti-tremelimumab antibodies was low (appendix p 4).

Subsequent anticancer treatment was received by 93 (24%) of 382 patients in the tremelimumab group and 58 (31%) of 189 patients in the placebo group (appendix p 7). Most of these patients received subsequent chemotherapy (90 [24%] patients in the tremelimumab group and 57 [30%] in the placebo group). No patients in either group received subsequent immune checkpoint inhibitors, such as anti-PD-L1/PD-1 agents.

Treatment-emergent adverse events of any grade were reported in 364 (96%) of 380 patients in the tremelimumab group and 179 (95%) of 189 patients who received placebo. Treatment-emergent adverse events of grade 3 or worse occurred in 246 (65%) patients in the tremelimumab group and 91 (48%) patients in the placebo group (table 3; appendix pp 8–12). The most common of these were dyspnoea (34 [9%] patients in the tremelimumab group *vs* 27 [14%] patients in the placebo group), diarrhoea (58 [15%] *vs* one [<1%]), and colitis (26 [7%] *vs* none). Treatment-related adverse events of any grade occurred in 278 (73%) patients in the tremelimumab group and 101 (53%) patients in the placebo group. Grade 3 or worse treatment-related adverse events occurred in 110 (29%) patients in the tremelimumab group and 12 (6%) patients in the placebo group. The most common of these were diarrhoea (55 [15%] patients in the tremelimumab group *vs* one [<1%] patient in the placebo group) and colitis (25 [7%] *vs* none). Concomitant steroid medication was administered to 237 (62%) patients in the tremelimumab group and 57 (30%) patients who received placebo.

Across both treatment groups, 303 (53%) of 569 patients had serious adverse events; 218 (57%) of 380 patients in the tremelimumab group and 85 (45%) of 189 patients receiving placebo (appendix pp 13–15). The most common serious adverse events (those present in ≥5% of patients in either group) were diarrhoea (69 [18%] patients receiving tremelimumab *vs* one (<1%) receiving placebo), dyspnoea (29 [8%] *vs* 24 [13%]), and colitis (24 [6%] *vs* none).

Treatment-emergent adverse events leading to study treatment discontinuation occurred in 104 (27%) of 380 patients in the tremelimumab group and 10 (5%) of 189 patients in the placebo group. The most common adverse events leading to discontinuation (those occurring in ≥1% of patients in the tremelimumab group) were diarrhoea (49 [13%] patients receiving tremelimumab *vs* one [<1%] patient receiving placebo), colitis (16 [4%] *vs* none), and vomiting (four [1%] *vs* none). Treatment-related adverse events leading to study treatment discontinuation occurred in 88 (23%) patients in the tremelimumab group and 4 (2%) patients in the placebo group. The most common treatment-related adverse events leading to discontinuation were diarrhoea (49 [13%] patients receiving tremelimumab *vs* one [<1%] patient receiving placebo) and colitis (16 [4%] *vs* none).

Adverse events leading to death occurred in 36 (9%) of 380 patients in the tremelimumab group and 12 (6%) of 189 patients in the placebo group (appendix p 16). Treatment-emergent adverse events leading to the death of more than one patient were mesothelioma (three [1%] patients in the tremelimumab group *vs* two [1%] in the placebo group), dyspnoea (three [1%] *vs* two [1%]); respiratory failure (one [<1%] *vs* three [2%]), myocardial infarction (three [1%] *vs* none), lung infection (three [1%] *vs* none), cardiac failure (one [<1%] *vs* one [<1%]), and colitis (two [<1%] *vs* none). Treatment-related adverse events leading to death occurred in five (1%) patients in the tremelimumab group and none in the placebo group. The causes of death were lung infection in one patient, intestinal perforation and small intestinal obstruction in one patient; colitis in two patients, and neuritis and skin ulcer in one patient.

The most common treatment-emergent adverse events of special interest (those occurring in >10% of patients) were diarrhoea and dermatitis (table 4). The adverse events of special interest (of any grade) that occurred in a larger proportion of patients (≥10% difference) in the tremelimumab group than in the placebo group were diarrhoea (180 [47%] patients *vs* 36 [19%] patients), dermatitis (169 [44%] *vs* 25 [13%]), and colitis or enterocolitis (39 [10%] patients *vs* no patients). Notable secondary events for enterocolitis or colitis included gastrointestinal perforation. Other serious sequelae included severe dehydration and acute renal insufficiency, metabolite abnormalities (either from diarrhoea or dehydration-induced acute renal insufficiency), blood loss from colitis, and anaemia requiring transfusion. Three patients who had *Clostridium difficile* infections, reported as adverse events or positive tests, continued to have diarrhoea or colitis after antibiotic treatment, and required further treatment with steroids to resolve the events. Grade 3 or worse endocrinopathy occurred in eight (2%) patients in the tremelimumab group and no patients in the placebo group. Elevations or reductions in thyroid-stimulating hormone outside the normal reference ranges (defined as ≥5 times ULN and ≤0·3 times lower limit of normal) were reported in 12 (3%) and 21 (6%) patients, respectively, in the tremelimumab group and in zero and one (<1%) patient in the placebo group.

| | Tremelimumab (n=382) | Placebo (n=189) |
|---|---|---|
| Objective response* | 17 (4·5%, 2·6–7·0) | 2 (1·1%, 0·1–3·8) |
| Best overall response | | |
| Confirmed complete response† | 0 | 0 |
| Unconfirmed complete response | 0 | 0 |
| Confirmed partial response† | 8 (2%) | 2 (1%) |
| Unconfirmed partial response | 9 (2%) | 0 |
| Stable disease (≥6 weeks after randomisation) | 104 (27%) | 41 (22%) |
| Progressive disease | 175 (46%) | 111 (59%) |
| Non-evaluable | 86 (23%) | 35 (19%) |
| Duration of response (months) | 4·8 (2·6–8·3) | 5·6 (2·8–8·3) |
| Disease control‡ | 106 (27·7%, 23·3–32·5) | 41 (21·7%, 16·0–28·3) |
| Durable disease control§ | 64 (16·8%, 13·1–20·9) | 22 (11·6%, 7·4–17·1) |

Data are n (%, 95% CI), n (%), or median (95% CI). 95% CIs were calculated with the exact probability method based on the binomial distribution. RECIST=Response Evaluation Criteria In Solid Tumors. *A best response of complete response or partial response. †Complete responses and partial responses that persist on repeat imaging study at least 4 weeks after the initial documentation of response. ‡A best response of complete response, partial response, or stable disease, which lasts for at least 12 weeks measured from date of randomisation. §A best response of complete response, partial response, or stable disease, which lasts for at least 6 months measured from date of randomisation.

***Table 2:*** **Antitumour responses assessed with RECIST in the intention-to-treat population**

## Discussion

The results of the DETERMINE study show that in this population of patients with previously treated relapsed pleural or peritoneal malignant mesothelioma, tremelimumab did not significantly improve overall survival compared with placebo. The findings for secondary efficacy outcomes, including progression-free survival, objective responses, and disease control, also showed no clinically meaningful differences between the tremelimumab and placebo groups. A higher proportion of patients in the tremelimumab group than in the placebo group had a treatment-emergent adverse event that was grade 3 or worse, serious, or led to discontinuation of study treatment. However, the safety profile of tremelimumab was consistent with the known safety profile of CTLA-4 inhibitors.

The study population in DETERMINE included patients with unresectable pleural and peritoneal malignant mesothelioma that had progressed after one or two previous systemic treatments for advanced disease. Although the treatment and prognoses of patients with advanced peritoneal and pleural

| | Tremelimumab (n=380) | | | | Placebo (n=189) | | | |
|---|---|---|---|---|---|---|---|---|
| | Grade 1–2 | Grade 3 | Grade 4 | Grade 5 | Grade 1–2 | Grade 3 | Grade 4 | Grade 5 |
| Any | 118 (31%) | 178 (47%) | 33 (9%) | 35* (9%) | 88 (47%) | 63 (33%) | 16 (8%) | 12 (6%) |
| Diarrhoea | 121 (32%) | 56 (15%) | 2 (<1%) | 0 | 35 (19%) | 1 (<1%) | 0 | 0 |
| Dyspnoea | 87 (23%) | 28 (7%) | 3 (<1%) | 3 (<1%) | 42 (22%) | 22 (12%) | 3 (2%) | 2 (1%) |
| Decreased appetite | 102 (27%) | 8 (2%) | 0 | 0 | 44 (23%) | 2 (1%) | 0 | 0 |
| Fatigue | 86 (23%) | 5 (1%) | 0 | 1 (<1%) | 55 (29%) | 5 (3%) | 0 | 0 |
| Nausea | 103 (27%) | 4 (1%) | 0 | 0 | 37 (20%) | 1 (<1%) | 0 | 0 |
| Constipation | 65 (17%) | 1 (<1%) | 0 | 0 | 51 (27%) | 2 (1%) | 0 | 0 |
| Pruritus | 100 (26%) | 3 (<1%) | 0 | 0 | 15 (8%) | 0 | 0 | 0 |
| Vomiting | 70 (18%) | 7 (2%) | 0 | 0 | 18 (10%) | 3 (2%) | 1 (<1%) | 0 |
| Cough | 67 (18%) | 0 | 0 | 0 | 30 (16%) | 1 (<1%) | 0 | 0 |
| Rash | 77 (20%) | 2 (<1%) | 0 | 0 | 13 (7%) | 0 | 0 | 0 |
| Musculoskeletal chest pain | 41 (11%) | 10 (3%) | 0 | 0 | 29 (15%) | 5 (3%) | 0 | 0 |
| Anaemia | 49 (13%) | 8 (2%) | 2 (<1%) | 0 | 20 (11%) | 3 (2%) | 0 | 0 |
| Asthenia | 45 (12%) | 9 (2%) | 0 | 1 (<1%) | 24 (13%) | 3 (2%) | 0 | 0 |
| Pyrexia | 59 (16%) | 3 (<1%) | 0 | 0 | 16 (8%) | 0 | 0 | 0 |
| Abdominal pain | 42 (11%) | 7 (2%) | 0 | 0 | 19 (10%) | 6 (3%) | 0 | 0 |
| Weight decreased | 46 (12%) | 2 (<1%) | 0 | 0 | 16 (8%) | 1 (<1%) | 0 | 0 |
| Colitis | 9 (2%) | 23 (6%) | 1 (<1%) | 2 (<1%) | 0 | 0 | 0 | 0 |
| Dehydration | 19 (5%) | 11 (3%) | 0 | 1 (<1%) | 1 (<1%) | 2 (1%) | 0 | 0 |
| Hypokalaemia | 18 (5%) | 9 (2%) | 0 | 0 | 3 (2%) | 1 (<1%) | 0 | 0 |
| Non-cardiac chest pain | 14 (4%) | 3 (<1%) | 0 | 0 | 5 (3%) | 5 (3%) | 1 (<1%) | 0 |
| Pneumonia | 9 (2%) | 6 (2%) | 3 (<1%) | 0 | 3 (2%) | 4 (2%) | 1 (<1%) | 1 (<1%) |
| General physical health deterioration | 8 (2%) | 8 (2%) | 1 (<1%) | 1 (<1%) | 5 (3%) | 2 (1%) | 0 | 0 |
| Ascites | 9 (2%) | 4 (1%) | 0 | 0 | 5 (3%) | 6 (3%) | 0 | 0 |
| Hyponatraemia | 5 (1%) | 10 (3%) | 0 | 0 | 5 (3%) | 2 (1%) | 1 (<1%) | 0 |
| Lipase increased | 7 (2%) | 9 (2%) | 2 (<1%) | 0 | 1 (<1%) | 3 (2%) | 0 | 0 |
| Pleural effusion | 7 (2%) | 4 (1%) | 1 (<1%) | 0 | 4 (2%) | 3 (2%) | 1 (<1%) | 0 |
| Pericardial effusion | 5 (1%) | 5 (1%) | 1 (<1%) | 1 (<1%) | 2 (1%) | 3 (2%) | 1 (<1%) | 0 |
| Pulmonary embolism | 5 (1%) | 4 (1%) | 4 (1%) | 1 (<1%) | 0 | 1 (<1%) | 2 (1%) | 0 |
| Respiratory failure | 0 | 1 (<1%) | 2 (<1%) | 1 (<1%) | 0 | 0 | 1 (<1%) | 3 (2%) |

Adverse events are reported in accordance with the Medical Dictionary for Regulatory Activities-preferred term. Grade 1–2 events occurring in ≥10% of patients in either treatment group and grade 3 or worse events occurring in ≥2% of patients in either treatment group are shown. Events are listed in order of descending frequency in the total population. Events are listed as indicated by the investigator on the case-report form; although some events (for example, fatigue and asthenia) might reflect the same condition, they are listed separately if they were reported by the investigators as two distinct events. Adverse events are reported up to and including 90 days after last day of dosing. Patients with multiple events in the same preferred term are counted only once for that preferred term. Patients with events in more than one preferred term are counted once for each preferred term. A table showing all grade 3 or worse treatment-emergent adverse events is included in the appendix (pp 8–12). *One patient in the tremelimumab arm died due to multiple grade 3 treatment-emergent adverse events, as well as multiple events that started more than 90 days after the last dose of tremelimumab, including a grade 5 event of haemoptysis; thus, this patient is not included in the number of patients with grade 5 treatment-emergent adverse events.

***Table 3:*** **Treatment-emergent adverse events**

mesothelioma are not identical, they are considered to be sufficiently similar to justify their inclusion in the same trial[22] and this approach was acceptable to the regulatory authorities during the trial set up. According to investigator assessments, very few patients in the study had stage I or II disease at study entry (<5%) and, despite the fact that roughly 25% had stage I–III disease (when patients can typically undergo resection), all patients were deemed to have unresectable disease by investigators at study entry.

The overall survival analysis had a high maturity; approximately 80% of patients had died at the time of data cutoff. Furthermore, the median overall survival in the placebo group (7·3 months) was consistent with the median overall survival that the sample size calculation was originally based on (ie, 7 months). This value was chosen on the basis of results from the phase 3 VANTAGE 014 study, which showed no significant difference in overall survival between vorinostat (7·1 months) and placebo (6·2 months) as second-line or third-line treatment for

pleural malignant mesothelioma.[23] Subsequent anticancer treatment was given to a small number of patients in DETERMINE and was mainly chemotherapy in both groups; thus, no evidence suggests a potential confounding effect of subsequent therapies on overall survival.

Progression-free survival data also had a high maturity; roughly 90% of patients had progressed or died at the time of data cutoff, and no clinically meaningful difference in progression-free survival was detected between the treatment groups. Evidence has shown that CTLA-4 blockade can lead to durable responses in melanoma.[24,25] However, we noted no clinically meaningful differences between treatment groups in disease control or durable disease control. Consistent with the known activity profile of CTLA-4 inhibitors,[12,13,26] a small proportion (<10%) of patients achieved an objective response in the tremelimumab group.

Treatment-emergent adverse events in the tremelimumab group, including grade 3 or worse adverse events, adverse events leading to death, and serious adverse events, were consistent with the known safety profile of CTLA-4 inhibitors,[12,13,26,27] were associated with the underlying disease, or both. As with other anti-CTLA-4 agents,[28] and in accordance with the two previous phase 2 single-arm trials of tremelimumab,[12,13] steroid use was central to the management of treatment-related side-effects.

The adverse events in patients receiving tremelimumab were similar to those reported for ipilimumab at a dose of 3 mg/kg every 3 weeks in stage III or IV unresectable melanoma.[26] In that ipilimumab trial, the median number of ipilimumab doses was four (ie, a median total dose of 12 mg/kg),[26] whereas a median of three doses of tremelimumab were administered in the current study (ie, a median total dose of 30 mg/kg). In the ipilimumab study,[26] the incidence of all-grade adverse events and grade 3 or worse adverse events typically associated with CTLA-4 inhibitors was similar to the incidence with tremelimumab in DETERMINE, with the exception of diarrhoea (47% of patients in the tremelimumab group and 19% with placebo in this study *vs* 33% and 5%, respectively, in the ipilimumab study). However, when a more similar dosing regimen of ipilimumab (10 mg/kg every 3 weeks) was reviewed against the tremelimumab 10 mg/kg dosing regimen used in this study, the incidence of diarrhoea and grade 3 or worse diarrhoea was similar between tremelimumab and ipilimumab.[29]

Gastrointestinal toxicities (diarrhoea and enterocolitis) were more common with tremelimumab than with placebo and notable secondary events for enterocolitis or colitis included gastrointestinal perforation, suggesting an association between tremelimumab and colitis or enterocolitis and perforation. In the tremelimumab group, clinically significant grade 3 or worse endocrinopathy occurred in a small number of patients (2%) and elevations in thyroid-stimulating hormone were reported in 3% of patients. Hypothyroidism and its associated symptoms develop over a prolonged period of time; thus, the small number of cycles of tremelimumab that were administered in the present study might have resulted in an underestimation of hypothyroidism with tremelimumab treatment. Consistent with the safety profile of CTLA-4 inhibitors, most endocrinopathy adverse events did not resolve, but were managed with steroids, hormone replacement therapy, or both. Hepatic toxicities occurred in both treatment groups and were mainly asymptomatic laboratory abnormalities, suggesting that tremelimumab is not associated with hepatic toxicity.

Tremelimumab showed encouraging clinical activity in two previous phase 2 studies in patients with pretreated pleural and peritoneal malignant mesothelioma.[12,13] Additionally, pharmacokinetic analysis suggested that the more intensive dosing schedule used in the second of these studies (MESOT-TREM-2012), and as used in DETERMINE, would maintain tremelimumab concentrations throughout the dosing interval at or above the target concentration of about 30 µg/mL.[13] Although results from these two trials should be placed in context, it is worth mentioning that both studies were small single-centre, single-arm trials, which could partly explain why these results did not translate into positive results in the multicentre, randomised DETERMINE study. Conversely, increased site experience with checkpoint inhibitor treatment and patients' comprehensive management in the course of therapy in the single-centre trials might also have partly contributed to the differences in outcomes between the two previous phase 2 studies and DETERMINE.

The incidence of anti-tremelimumab antibodies in patients receiving tremelimumab in this study was low; thus, immunogenicity was unlikely to have been responsible for the lack of observed efficacy. The high

| | Tremelimumab (n=380) | | Placebo (n=189) | |
|---|---|---|---|---|
| | Any grade | Grade 3 or worse | Any grade | Grade 3 or worse |
| Diarrhoea | 180 (47%) | 59 (16%) | 36 (19%) | 1 (<1%) |
| Dermatitis | 169 (44%) | 9 (2%) | 25 (13%) | 0 |
| Colitis or enterocolitis | 39 (10%) | 29 (8%) | 0 | 0 |
| Endocrinopathy | 32 (8%) | 8 (2%) | 3 (2%) | 0 |
| Hepatitis or hepatic toxic effects | 24 (6%) | 8 (2%) | 10 (5%) | 1 (<1%) |
| Renal failure and nephritis | 24 (6%) | 4 (1%) | 5 (3%) | 0 |
| Pancreatitis | 23 (6%) | 14 (4%) | 7 (4%) | 4 (2%) |
| Hypersensitivity reaction, anaphylaxis, or infusion reaction | 11 (3%) | 1 (<1%) | 4 (2%) | 0 |
| Pneumonitis or interstitial lung disease | 3 (<1%) | 1 (<1%) | 0 | 0 |
| Neuropathy or neuromuscular toxic effects | 2 (<1%) | 2 (<1%) | 0 | 0 |

Adverse events are reported up to and including 90 days after last day of dosing. Patients with multiple events in the same adverse events of special interest category are counted only once in that category. Patients with events in more than one adverse events of special interest category are counted once in each category. The preferred terms for each category of adverse events of special interest are listed in the appendix (pp 2–3).

***Table 4:*** **Treatment-emergent adverse events of special interest**

concomitant steroid use by patients in the active treatment group compared with the placebo group might have affected the efficacy of tremelimumab in this study, although no data from other immune checkpoint blockade studies suggest a link between steroid use and reduced antitumour activity.[30]

Immune checkpoint inhibitors are speculated to be more effective in tumours with higher mutational loads and therefore greater numbers of neoantigens, as suggested by data from studies in lung cancer[31] and the high mutational load detected in melanomas and Lynch-syndrome-associated tumours.[32] An analysis of the malignant mesothelioma genome established that the load of somatic mutations is low in this type of cancer.[33] Thus, the absence of an overall survival benefit in DETERMINE could be a result of the low mutational load in malignant mesothelioma. A further explanation could be that the highly immunosuppressive environment in malignant mesothelioma[7] might preclude immune activation in response to tremelimumab therapy. The absence of a predictive biomarker for CTLA-4 blockade means that identification of patients more likely to respond to tremelimumab and other CTLA-4 inhibitors is challenging and more research is required in this area.

The results of the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS) showed that bevacizumab added to cisplatin and pemetrexed significantly improves overall survival compared with cisplatin and pemetrexed alone in newly diagnosed pleural mesothelioma.[4] Although second-line pemetrexed has been shown to improve progression-free survival and disease control over best supportive care in previously treated malignant mesothelioma where pemetrexed had not been used in the first-line setting,[34] no randomised phase 3 study has yet shown a significant improvement in overall survival in second-line malignant mesothelioma in the post-pemetrexed setting.[23,34]

To our knowledge, DETERMINE is the first randomised immune checkpoint inhibitor study in malignant mesothelioma. Its double-blind design and large sample size are important strengths; however, the study also had some limitations. Patients had limited exposure to study treatment (median of three doses), which might have been a consequence of the advanced disease in this trial population, given that the median number of doses and treatment duration were the same in both groups. Because of the low percentage of patients in the study with peritoneal disease (<5%), review of overall survival by anatomic site (a key stratification factor) via subgroup analysis was not possible. Additionally, interpretation of patient-reported outcome data was limited by the absence of patient-reported outcome data collection beyond the end of treatment or discontinuation.

The rapid accrual to the DETERMINE trial underscores the urgent and unmet need for new treatment options for patients with malignant mesothelioma and for further research to identify alternative therapeutic strategies. Anti-PD-1 and anti-PD-L1 monotherapies have shown preliminary signs of clinical activity in malignant mesothelioma;[35–37] thus, combining antibodies that target the PD-1/PD-L1 pathway and the CTLA-4 pathway could provide additional therapeutic benefit. Indeed, combined CTLA-4 and PD-L1 blockade has been reported to enhance antitumour activity compared with single-agent blockade in preclinical models,[38] and has also shown a manageable safety profile and preliminary signs of antitumour activity in patients with advanced non-small-cell lung cancer.[39,40] Multiple immune checkpoint blockade combination regimens are currently under investigation in malignant mesothelioma,[41] including tremelimumab with the anti-PD-L1 agent durvalumab in the phase 2, open-label, single-arm NIBIT-MESO-1 study (NCT02588131).

#### Contributors

MM, AST, PKS, and HLK contributed to the study design. AS, LC, PKS, and HLK collected, analysed, and interpreted the data. KN, DK, SJA, and AKN collected and interpreted the data. SCP, AB, PT, and FG collected the data. MM, JA, AST, MT, and MP analysed and interpreted the data. All authors drafted the manuscript and approved the final draft.

#### Declaration of interests

MM has received personal fees for advisory board membership and a research grant for his institution, both outside the submitted work, from AstraZeneca. AS has received personal fees for advisory board membership from AstraZeneca during this study and from Bristol-Myers Squibb, Roche, and MSD, outside the submitted work. JA reports grant funding from Bristol-Myers Squibb, and Roche, and personal fees from Eli Lilly, Bristol-Myers Squibb, Roche, and Boehringer Ingelheim, outside the submitted work; in addition, he holds a licensed patent for an allogenic tumour cell lysate. KN has received financial support from MedImmune during this study to run trials, indirectly via his institution. DAF has received personal fees for advisory board membership from AstraZeneca, Bayer, and Aduro; financial clinical trial support from Bristol-Myers Squibb and Cancer Research UK; and research funding from Pierre Fabre and Astex; all outside the submitted work. AST reports grant funding from Boehringer Ingelheim, Bristol-Myers Squibb, Merck, Takeda Oncology, Seattle Genetics, Epizyme, ARIAD Pharmaceuticals, and Polaris Pharmaceuticals; she has served on advisory committees for AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, EMD Serono, Genentech Bio-Oncology, Merck, Eli Lilly, Novartis Pharmaceuticals Corporation, and Roche Laboratories; and has consulting agreements with Eli Lilly, Novartis Pharmaceuticals Corporation, and Roche Laboratories, all during this study. SJA has received personal fees for advisory board membership from AstraZeneca during this study. AKN has received clinical trial funding from AstraZeneca and personal fees for clinical trial consulting from Boehringer Ingelheim, Aduro, Bayer, and Sellas Life; she has also served on a data safety monitoring board for Epizyme and has received personal fees from Roche for clinical trial management committee membership; all outside the submitted work. MT, MP, and PKS are employees of AstraZeneca; MT and PKS hold shares in AstraZeneca. HLK has received research funding from AstraZeneca and MedImmune during this study, and has served on advisory boards for AstraZeneca and MedImmune outside the submitted work. All other authors declare no competing interests.

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