Interleukin-1α neutralisation in patients with cancer

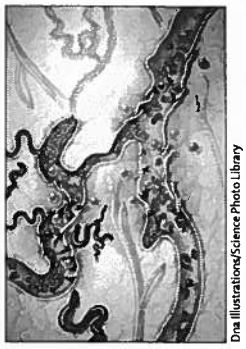
Inflammation contributes to the severity of most diseases, and cytokine-specific blocking treatments are well established for autoinflammatory and autoimmune diseases.[1] However, cytokine-mediated inflammation also has a role in the pathogenesis of cancer; for example, in the immunosuppression of the disease.[2] Cytokine-mediated systemic inflammation is also a debilitating aspect of cancer. Many tumours produce inflammatory cytokines, which promote angiogenesis and tumour growth. Therefore, blocking a cytokine is a therapeutic option for treatment of cancer, particularly since anti-cytokine treatment lacks side-effects and tumours are unlikely to develop resistance to cytokine blockade. In *The Lancet Oncology*, David Hong and colleagues[3] report the effects of neutralising interleukin-1α in patients with end-stage cancers of various origins. The study is a unique contribution because it opens entire new areas in cancer therapeutics. The study also provides a rationale for early use of anti-cytokine therapy in cancer and sets the stage for use of anti-cytokine treatment in combination with kinase inhibitors and anti-immunosuppressive treatments.

Although blocking the interleukin-1 receptor with anakinra reduces the progression of smouldering myeloma into overt myeloma,[4] patients with epithelial cancers are rarely treated with specific anti-cytokine drugs such as those that block interleukin-1.[5] A prevailing, but misunderstood, notion is that blocking an immuno-stimulating cytokine such as interleukin-1 would reduce the ability of the immune system to kill cancer cells and would therefore be contraindicated. However, since reversal of immunosuppression rather than stimulation of immune responses in cancer has been validated by blocking cytotoxic T-lymphocyte antigen 4 (CTLA4) and programmed cell death 1 (PD-1), there is less reluctance to neutralise an immunostimulatory cytokine such as interleukin-1α. Nevertheless, in what may be a landmark study, patients with various refractory end-stage cancers and who were losing weight received a course of MAPp1, a naturally occurring human neutralising interleukin-1α antibody.[3] After treatment, a significant number of patients responded, with an increase in lean body mass (p=0·02), decreased constitutional symptoms (fatigue p=0·008, pain p=0·025, and appetite loss p=0·020), and extended survival compared with baseline.

The study, albeit small, is the first to specifically neutralise interleukin-1α, a highly inflammatory member of the interleukin-1 family. It is a unique contribution to the literature for many reasons, particularly in end-stage cancer. Since blocking the interleukin-1 receptor with anakinra or neutralising interleukin-1β with canakinumab or rilonacept are without symptomatic adverse events,[1] it is not surprising that there were no adverse events with MABp1. Importantly, findings from the study point to the need to investigate likely mechanisms of action of MABp1. First, the data show that treatment reduces systemic inflammation since a decrease in circulating interleukin-6 concentrations remains one of the most consistent findings of interleukin-1 blockade,[1] although in this study, the reduction was only significant in patients who also gained lean body mass. The source of the inflammatory trigger is probably the tumour itself, because all cancer cells of epithelial cell origin contain interleukin-1α in its precursor form. Inflammation is also caused by invasion of the tumour microenvironment by stromal cells. As tumours outgrow their vascular supply, they become necrotic and the interleukin-1α precursor is readily released, which triggers local production of chemokines, facilitating an influx of neutrophils and monocytes.[1] Unlike the precursor of interleukin-1β, the interleukin-1α precursor is fully active. Neutralisation of local interleukin-1α probably reduces the infiltration of tumour-associated macrophages and myeloid-derived suppressor cells, which contribute to the immunosuppression of cancer.[2]

At some point, this local inflammation must have become systemic to account for one of the post-hoc exploratory outcomes of the study: evidence of a non-specific increase in survival (19·3 months) in patients with colorectal cancer and increased lean body mass compared with those who lost lean body mass (6·6 months; p=0·098). The association of inflammation not caused by cancer with loss of lean body mass is well established, and interleukin-1 can directly induce muscle protein breakdown.[6]

Hong and colleagues[3] also reported a reduction in fatigue, which is consistent with the use of anakinra in patients with inflammatory diseases.[1] In the early 1990s, interleukin-1β or interleukin-1α was administered to



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patients with chemotherapy-suppressed bone marrow to stimulate haematopoiesis; although effective, picomolar concentrations of interleukin-1α were toxic, causing fever, severe fatigue, loss of appetite, myalgia, and hypotension.[7]

From findings of the aforementioned studies and other studies on human responses to picomolar concentrations of interleukin-1, the notion that blocking this cytokine would reduce the severity of inflammatory diseases became clear. However, the rationale for blocking interleukin-1α in any disease should not be based on raised circulating serum concentrations since interleukin-1α is not released from living cells and is active as an integral cell-surface protein. Interleukin-1α is also present on platelets, which probably accounts for the systemic effects such as increased interleukin-6 concentrations. In fact, the longstanding reports of platelet involvement in metastasis, which include platelet–endothelial cell interaction,[8] will probably now be partly understood by neutralisation of interleukin-1α. The study by Hong and colleagues[3] provides clinical evidence that endogenous interleukin-1α-induced interleukin-6 contributes to thrombocytosis in cancer.[7]

Additional possible mechanisms of action with neutralisation of interleukin-1α include decreased angiogenesis[9] and decreased immunosuppression.[10] Interleukin-1α neutralisation also directly affects the tumour by inhibition of tumour growth. With the interleukin-1α precursor present in non-cancerous and most cancerous cells, and in view of the broad inflammatory properties of interleukin-1α, no one mechanism can account for the study's findings.[3]

We are left with many questions. Is progressive loss in lean body mass a sufficient reason to initiate treatment with interleukin-1α neutralisation? In view of the near total absence of attributable adverse events, the long-term safety of interleukin-1 blockade,[1] and the efficacy of MABp1, it might be possible to use this antibody early in treatment schema. Would neutralisation of interleukin-1α be more effective if used earlier as an adjunct during chemotherapy? For example, would neutralisation of interleukin-1α potentiate the antitumour effect of tyrosine kinase inhibitors? Since interleukin-1 induces myeloid suppressor cells,[2] would neutralisation of interleukin-1α be beneficial if used in combination with anti-CTLA4 or anti-PD-1? Further testing of MABp1 in clinical trials will provide the answers to these questions and help to address a particularly debilitating symptom of cancer, chronic inflammation.

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MABp1, a first-in-class true human antibody targeting interleukin-1α in refractory cancers: an open-label, phase 1 dose-escalation and expansion study

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Summary

Background Inflammation is an important feature of the malignant phenotype and promotes angiogenesis, tumour invasiveness, metastases, and cachexia. We used a first-in-class, monoclonal antibody (MABp1) cloned from a human being to target interleukin-1α, a mediator of chronic inflammation. We aimed to assess the safety and tolerability of MABp1 for interleukin-1α blockade in a refractory cancer population.

Methods We did an open-label, dose-escalation, and phase 1 study of MABp1 in adults with metastatic cancer at the MD Anderson Clinical Center for Targeted Therapy (Houston, TX, USA). We used a standard 3+3 design to identify the maximum tolerated dose. Patients received MABp1 intravenously once every 3 weeks through four dose levels: 0·25 mg/kg, 0·75 mg/kg, 1·25 mg/kg, and 3·75 mg/kg. After the dose-escalation phase, a second dosing arm was started with dosing every 2 weeks at the maximum tolerated dose. The primary objectives were safety, tolerability, characterisation of the pharmacokinetic profile, and identification of the recommended phase 2 dose. Secondary endpoints included pharmacodynamic effects and antitumour activity. All patients who received at least one dose of MABp1 were included in the safety analyses. This trial is registered with ClinicalTrials.gov, NCT01021072.

Findings Between March 15, 2010, and July 30, 2012, 52 patients with metastatic cancer (18 tumour types) received anti-interleukin-1α monotherapy in dose-escalation and expansion groups. MABp1 was well tolerated, with no dose-limiting toxicities or immunogenicity. Thus, the recommended phase 2 dose was concluded to be 3·75 mg/kg every 2 weeks. Pharmacokinetic data were consistent at all dose levels and showed no evidence of accumulation or increased clearance of MABp1 at increasing doses. For 42 assessable patients, median plasma interleukin-6 concentrations had decreased from baseline to week 8 by a median of 2·7 pg/mL (IQR −12·6 to 3·0; p=0·08). Of the 34 patients restaged, one patient had a partial response and ten had stable disease. 30 patients were assessable for change in lean body mass, which increased by a mean of 1·02 kg (SD 2·24; p=0·02) between baseline and week 8. The most common adverse events possibly related to the study drug were proteinuria (n=11; 21%), nausea (7; 13%), and fatigue (7; 13%). The most frequent grade 3–4 adverse events (regardless of relation to treatment) were fatigue (3; 6%), dyspnoea (2; 4%), and headache (2; 4%). Two patients (4%) had grade 5 events (death due to disease progression), which were unrelated to treatment.

Interpretation MABp1 was well tolerated, no dose-limiting toxicities were experienced in this study, and disease control was observed. Further study of MABp1 anti-interleukin-1α antibody therapy for advanced stage cancer is warranted.

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Introduction

The potential to treat cancer by blocking pathological inflammation has resulted in many clinical trials with anti-inflammatory drugs. Inflammation is responsible for pleiotropic actions such as angiogenesis, tumour stromal remodelling, tumour invasiveness, metastasis, and cachexia. Thus, inflammation is a crucial feature of the malignant phenotype of cancer. Targeting inflammation could alter the way cancer is managed—particularly in advanced, refractory disease, in which morbidity from cytotoxic drugs outweighs treatment benefit. However, identification of a pharmacological target that effectively modulates cancer-associated inflammation has been difficult. Non-steroidal anti-inflammatory drugs have not exhibited sufficiently potent or specific activity.[1] Other drugs, such as targeted anti-VEGF treatment, might act too far downstream in the inflammatory cascade to be particularly effective.

Interleukin-1α is a very early—and perhaps universal—step in the sterile inflammatory response at the centre of the malignant phenotype.[2] Its presence on leucocytes and platelets drives processes such as tumour angiogenesis and tissue matrix remodelling.[3–5] In the context of its deregulated expression on malignant tumours, interleukin-1α is associated with dedifferentiated, aggressive disease.[6–8]

Interleukin-1α on platelets might be a particularly important target for treatment of cancer. Platelet-associated

interleukin-1α can stimulate the vascular endothelium, driving an early step in vascular activation and infiltration of pro-tumour inflammatory cells into the tumour microenvironment. Increasing platelet counts in patients with advanced cancer are a prognostic indicator of worse survival.[9] Platelets might also be involved in haematogenous spread of tumours, and a role for interleukin-1α in this process has been suggested.[10–13] Interleukin-1α on tumour–platelet microemboli might provide interleukin-1 agonist activity in the microvasculature of the hypothalamus, where interleukin-1 receptor signalling mediates cachexia but where the origin of the signalling is unknown.[14,15]

High-affinity antibodies are not germline encoded, but rather are derived through recombination and somatic hypermutation of genomic DNA. Gene rearrangement creates antibodies with protein sequences unique only to the B lymphocyte that rearranged the gene. Since mature antibody sequences are not encoded in the germline, they can be regarded as foreign proteins, similar to an infectious agent or another substance that is foreign to the body. Thus, nascent antibody-producing B lymphocytes undergo a selection and deletion process, which is necessary to ensure that antibodies bind to their target with high affinity (ie, selection), but are not otherwise incompatible to the host (ie, deletion). Reproduction of selection and deletion conditions outside the human milieu is not possible. The use of the term fully human to describe many marketed therapeutic antibodies has created confusion regarding the source of these antibodies. There are no true human antibodies marketed at present—all marketed antibodies so far described as fully human have undergone in-vitro affinity maturation to improve activity.

MABp1 is a natural antibody, cloned from an affinity-matured, in-vivo human immune response, with no sequence modifications to alter binding affinity. This first-in-class true human monoclonal antibody specifically targets interleukin-1α. We aimed to assess the safety, tolerability, and efficacy of interleukin-1α blockade in a refractory cancer population.

Methods

Patients

For the **trial protocol** see http://www.xbiotech.com/downloads/MABP1_Advanced_Cancers_Protocol.pdf

We did an open-label, dose-escalation study of MABp1 in patients with metastatic cancer. Patients with pathologically confirmed metastatic disease that was refractory to standard treatments (or with a malignancy for which no standard treatment exists) were screened at MD Anderson Clinical Center for Targeted Therapy (Houston TX, USA). Eligible patients were at least 18 years of age; had an Eastern Cooperative Oncology Group (ECOG) score of 0, 1, or 2; and had adequate haematological (absolute neutrophil count of $\geq 1{\cdot}5 \times 10^9$/L, platelet count of $\geq 100 \times 10^9$/L, and haemoglobin count of ≥90 g/L), renal (serum creatinine ≤1·5 times the upper limit of normal [ULN]), and hepatic function (total bilirubin ≤1·5 times the institutional ULN and alanine aminotransferase ≤2·0 times the institutional ULN, except for patients with primary liver tumours or known liver metastases, for whom adequate alanine aminotransferase was classed as ≤3·0 times the institutional ULN). Patients with serious uncontrolled medical disorders, active infections, or symptomatic brain metastases were excluded. Other exclusion criteria were uncontrolled or significant cardiovascular disease; dementia or an altered mental status that would prohibit the understanding or rendering of informed consent; patients who had not recovered to grade 1 or lower adverse effects of previous treatment at the time of enrolment (excluding alopecia); patients who had received extensive radiation therapy to the bone marrow; immunocompromised patients, including those known to be infected with HIV; patients with a history of hypersensitivity to compounds of similar chemical or biological composition to MABp1; women who were pregnant or breastfeeding; and women of childbearing potential or men whose sexual partners are women of childbearing potential who are unwilling or unable to use an acceptable method of contraception. A washout period of 4 weeks since the last dose of chemotherapy, biological or targeted therapy, radiation therapy, or surgery was required before receiving the study drug. The study was approved by MD Anderson's Institutional Review Board, and written informed consent was obtained from each patient before enrolment. The Institutional Review Board reviewed the potential benefit of treatment versus the risk in this patient group.

Procedures

MABp1, a true human IgG1κ monoclonal antibody specific for human interleukin-1α, was provided by XBiotech USA (Austin, TX, USA). The antibody was derived from Epstein-Barr-virus-immortalised B lymphocytes derived from an individual with circulating anti-interleukin-1α, as described by Garrone and colleagues.[16] Somatic hypermutation suggested affinity maturation in vivo. Extensive preclinical characterisation of the antibody showed that it specifically neutralises interleukin-1α, prevents binding to interleukin-1 receptor type 1, and blocks biological activities in vitro.

We used a standard 3+3 design to identify the maximum tolerated dose. Patients received MABp1 intravenously once every 3 weeks through four dose levels: 0·25 mg/kg, 0·75 mg/kg, 1·25 mg/kg, and 3·75 mg/kg. The infusion time was 1 h. There was no maximum number of treatment cycles; instead, patients could continue on study until they experienced radiographic or clinical disease progression. Patients with disease progression discontinued the study and were followed up for 30 days after discontinuation.

Patient safety was assessed weekly for the first 8 weeks, and then on day 1 of each cycle thereafter. Dose escalation was continued until dose-limiting toxicities or until the

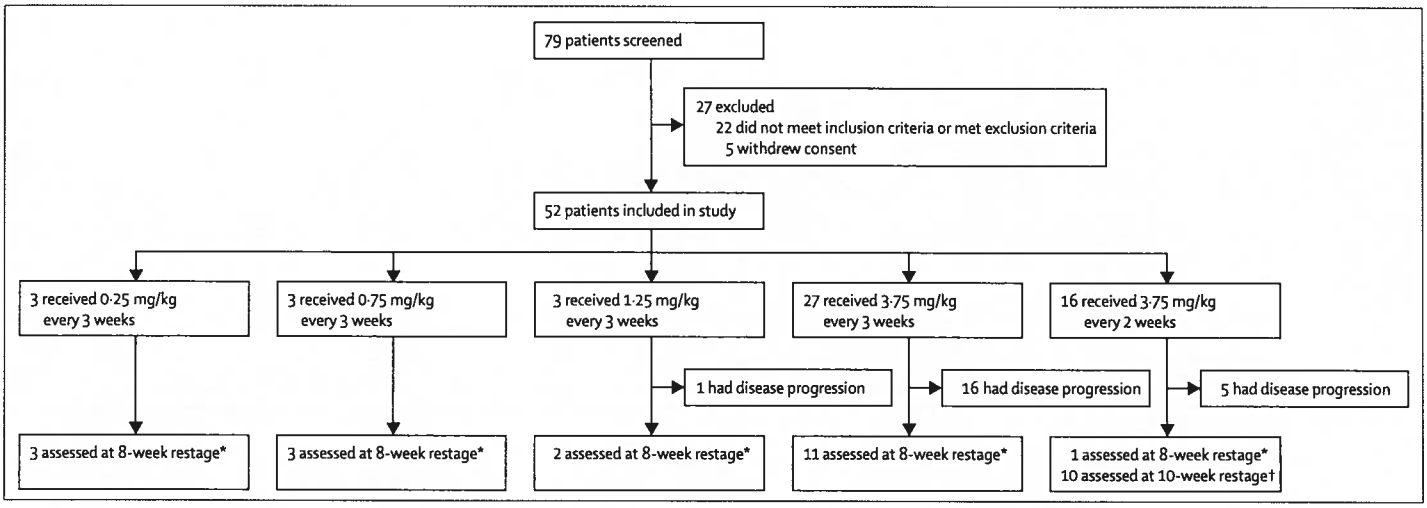

Figure 1: **Trial profile**
*Using the Response Evaluation Criteria in Solid Tumours. †Using the Immune Related Response Criteria.

highest planned dose level was reached without any dose-limiting toxicities. We defined dose-limiting toxicities as any grade 3 or greater haematological or non-haematological toxicity, as assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0), that occurred during any cycle of treatment and that was deemed to be possibly, probably, or definitely associated with the study drug. If dose-limiting toxicities occurred in at least 33% of patients at any given dose level then that dose was classed as above the maximum tolerated dose. During the 3+3 dose escalation, if a dose-limiting toxicity occurred in one of the three patients, then three more patients were added at that dose. If two of six had a dose-limiting toxicity, then that dose level was declared to be above the maximum tolerated dose. After the dose-escalation phase, a second dosing arm was started with dosing every 2 weeks at the maximum tolerated dose. Serious adverse events were defined as death; a life-threatening adverse event; inpatient hospital admission or prolongation of existing hospital stay; a persistent or substantial incapacity or substantial disruption of the ability to undertake normal life functions; a congenital anomaly or birth defect; or an important medical event that in the investigator's medical judgement may need medical or surgical intervention to prevent one of the outcomes listed in this definition.

The study had no prospective enrolment limitations, but instead was designed to allow increased enrolment for the purpose of assessment of safety and efficacy. Enrolment was concluded after completion of expansion cohorts and after the assessment of efficacy.

Blood samples were collected from patients at baseline before infusion of MABp1; on days 1, 8, and 15 of the first three cycles for 3-weekly dosing; on days 1 and 8 of the first four cycles of 2-weekly dosing; and on day 1 of each cycle thereafter. Platelet counts were measured as part of routine blood analysis. Flow cytometry was used to measure expression of CD14, CD16, and interleukin-1α on peripheral blood mononuclear cells by a FACSCalibur Flow Cytometer (BD Biosciences, San José, CA, USA. The clones used were PE anti-human CD16 (5 µL per stain; eBioscience 12-0168; clone CB16) for CD16, PerCP-Cy5.5 anti-human CD14 (5 µL [0·5 µg] per stain; eBioscience 45-0149; clone 61D3) for CD14, and 110609M1 (2·05 mg/mL, 0·25 µg per stain) for MABp1biotin.). Interleukin-1α is primarily a cell-surface-associated cytokine, and circulating levels of interleukin-1α are thus are very low. Therefore, changes in serum concentration of interleukin-6 were measured as a biomarker for anti-interleukin-1α activity.[2] High-sensitivity C-reactive protein, which is also a surrogate marker of inflammation, was measured at the clinical laboratory at MD Anderson Cancer Center. Interleukin-6 concentrations were measured with ELISA (R&D Systems, Minneapolis, MN, USA). Human plasma (100 µL) was loaded in duplicate wells, and assays were done according to the manufacturer's instructions. The minimum detectable interleukin-6 concentration was 0·70 pg/mL.

To assess immunogenicity, anti-drug antibody responses were measured using a proprietary sandwich ELISA developed by XBiotech. Patient plasma was incubated on MABp1-coated microplates followed by labelled secondary antibodies. Measurements were taken at the same timepoints as for pharmacokinetic data.

Tumour response was assessed every 8 weeks using the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 for patients with solid tumours who entered the study before a protocol amendment on Feb 15, 2012. Details of the Immune Related Response Criteria (ir-RC) were first published shortly after the trial protocol was submitted for regulatory approval. Based on the proposed mechanism of action, we hypothesised that the ir-RC might be better suited for assessment of the antineoplastic

activity of MABp1, and therefore amended the protocol accordingly. For patients who entered the study thereafter, tumour response was assessed every 10 weeks using the Immune Related Response Criteria (ir-RC).[17] In the event that a patient experienced clinical progression before the first restaging timepoint, patients were asked to undergo radiographic restaging at the time of progression. Those who complied with this restaging were included in the response analysis.

Lean body mass measurements were done using dual energy x-ray absorptiometry (DEXA) at baseline (≤2 weeks before the start of treatment) and at 8 weeks after the first antibody dose.[18,19] DEXA measures bone mineral density, lean body mass, and fat mass. Patient wellbeing was assessed on day 1 of each cycle using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ C30; version 3.0), a 30-item questionnaire consisting of three scales: functional (physical, role, emotional, social, and cognitive), symptom (fatigue, nausea and vomiting, and pain), and global quality of life (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties). The global quality of life score was calculated using the raw score. Responses to all the individual items in the functional and symptom scales are transformed to a linear scale before analysis and the final score ranges from 0 to 100. Higher scores represent a higher level of functioning and healthier quality of life, whereas lower scores suggest a reduction in symptom level. Resting energy expenditure was measured at baseline and week 8 in the morning after a minimum 8-h overnight fast by indirect calorimetry with a MedGem calorimetry device (Microlife USA, Clearwater, FL, USA).

	Patients (n=52)
Age (years)	61 (52–67)
Sex	
Women	28 (54%)
Men	24 (46%)
Ethnic origin	
White	40 (77%)
African-American	4 (8%)
Hispanic	5 (10%)
Asian	3 (6%)
Weight (kg)	
Mean (SD)	68 (16)
Median (IQR)	65 (58–80)
Body-mass index (kg/m²)	
Mean (SD)	24·5 (4·8)
Median (IQR)	24·1 (21·2–26·1)
C-reactive protein (nmol/L)	140·96 (32·38–556·20)
ECOG grade	
0	15 (29%)
1	32 (62%)
2	5 (10%)
Tumour type	
Non-small-cell lung cancer	17 (33%)
Colorectal	14 (27%)
Pancreatic	2 (4%)
Renal cell cancer	2 (4%)
Castleman's	2 (4%)
Nasopharyngeal	2 (4%)
Thyroid	2 (4%)
Other	11 (21%)
Number of previous chemotherapy regimens	5 (2·4)

Data are median (IQR), number (%), or mean (SD). Some percentages do not total 100 because of rounding. ECOG=Eastern Cooperative Oncology Group.

Table 1: **Demographics, baseline characteristics, and tumour types**

Outcomes

The primary objectives were assessment of the safety and tolerability of MABp1, characterisation of the pharmacokinetic profile, and identification of the recommended phase 2 dose. Safety and tolerability were assessed by change in routine safety laboratory assessments and monitoring of adverse events. Secondary objectives were assessment of pharmacodynamic effects (changes in interleukin-6, monocyte, and platelet cell counts), antitumour activity, cancer-related cachexia symptoms, and change in quality of life.

Statistical analysis

All patients who received at least one dose of MABp1 were included in the safety analysis. All patients with data on DEXA and EORTC measures at baseline and 8 weeks were included in lean body mass and quality of life analyses. No adjustments were made for missing data. Demographics, baseline characteristics, and safety variables were summarised by descriptive statistics; continuous variables were reported as mean (SD), or median (IQR) if non-normal. Categorical variables were reported as number of cases (%). We did an equivalency test on platelet counts arising from paired-sample data (baseline and week 8) with a 5% margin of equivalence. We also did an exploratory post-hoc analysis to assess the baseline to week 8 change in platelet counts and to estimate the cumulative survival probabilities according to lean body mass response. We did paired *t* tests (Wilcoxon signed-rank test for non-normal data) to compare the significance of differences between parameters. Survival analyses were done by the Kaplan–Meier product-limit method. The log-rank test was used to compare cumulative survival across groups. All data were analysed with SAS version 9.2. This study is registered with ClinicalTrials.gov, number NCT01021072.

Role of the funding source

The sponsor designed the study with input from the investigators. The study sponsor was also involved in data collection, data analysis, data interpretation, and writing of the report. All authors had full access to all the

data in the study, and the corresponding author had final responsibility for the decision to submit for publication.

Results

Between March 15, 2010, and July 30, 2012, 79 patients were screened: 22 were not enrolled in the study on the basis of protocol inclusion or exclusion criteria and five withdrew consent during the screening period (figure 1). 52 patients with 18 different malignancies were enrolled and treated. Median follow-up was 228 days (IQR 92–436). Three patients were treated at each of the first three dose escalation levels (0·25 mg/kg, 0·75 mg/kg, and 1·25 mg/kg every 3 weeks), 27 were treated at 3·75 mg/kg every 3 weeks, and 16 were treated at 3·75 mg/kg every 2 weeks (figure 1). Non-small-cell lung cancer (NSCLC) was the most represented tumour type followed by colorectal carcinoma (table 1).

Over 300 infusions were administered without any infusion reactions. No patients needed dose reductions or delays for toxicity, no patients discontinued treatment for toxicity, and there were no treatment-related deaths. Thus, the maximum tolerated dose was not reached. The highest dose administered was declared the recommended phase 2 dose (3·75 mg/kg every 2 weeks).

There were no reactions reported that were probably or definitely related to the study drug. There was one serious adverse event listed as possibly drug related: pneumonia in a patient with NSCLC. The most common adverse events possibly related to the study drug were proteinuria in 11 patients (21%; all grade 1–2), nausea in seven patients (13%; all grade 1–2), and fatigue in seven patients (13%; six grade 1–2 and one grade 3). Of the 11 patients with proteinuria deemed to be possibly related to study drug, four had grade 2 proteinuria and the remaining seven had grade 1 proteinuria; however, grade 1 proteinuria as measured by urine dipstick has a poor positive predictive value for true albuminuria as measured by 24-h urine collection.[20] There were no other study-drug-related adverse events with more than 10% frequency. The most frequent grade 3–4 adverse events that occurred in the entire study population (which were not necessarily associated with study drug) were fatigue (n=3; 6%), dyspnoea (n=2; 4%), and headache (n=2; 4%, table 2). Two patients (4%) had grade 5 events (death due to disease progression), which were deemed to be unrelated to treatment.

Pharmacokinetic data for MABp1 serum concentrations were consistent at all dose levels (table 3). The mean and maximum concentrations showed no evidence of accumulation or increased clearance, with little change from the initial dosing on cycle 1 day 1 to the third dosing at cycle 3 day 1 (day 42 in the 3-week cycles and day 28 in the 2-week cycles). A half-life of about 3 days was noted at each dose level (data not shown). The coefficient of variation between patients was consistent with previous reports for therapeutic antibodies.[21] Anti-drug antibodies were not present after over 300 infusions (data not shown).

	Grade 1–2	Grade 3	Grade 4	Grade 5
Fatigue	12 (23%)	2 (4%)	1 (2%)	0
Proteinuria	12 (23%)	0	0	0
Anorexia	9 (17%)	0	0	0
Nausea	9 (17%)	1 (2%)	0	0
Constipation	6 (12%)	1 (2%)	0	0
Dyspnoea	5 (10%)	2 (4%)	0	0
Hyperkalaemia	5 (10%)	0	0	0
Hypoalbuminaemia	5 (10%)	0	0	0
Vomiting	5 (10%)	0	0	0
Acute kidney injury	1 (2%)	1 (2%)	0	0
Anaemia	3 (6%)	1 (2%)	0	0
Increased aspartate aminotransferase	1 (2%)	1 (2%)	0	0
Baseline thrombocytopenia	0	1 (2%)	0	0
Focal seizure of the tongue	0	1 (2%)	0	0
Generalised weakness	0	1 (2%)	0	0
Headache	2 (4%)	1 (2%)	1 (2%)	0
Intractable pain	0	1 (2%)	0	0
Lymphocytopenia	2 (4%)	1 (2%)	0	0
Problem awakening from sedation for MRI	0	1 (2%)	0	0
Uncontrolled pain	0	1 (2%)	0	0
Leg cramps	0	0	1 (2%)	0
Diarrhoea	3 (6%)	0	1 (2%)	0
Ear irritation	0	0	1 (2%)	0
Muscle cramp	0	0	1 (2%)	0
Progression of disease leading to death	0	0	1 (2%)	2 (4%)

Data are number of patients (%).

Table 2: **Most frequent adverse events, regardless of posited relation to drug**

	Cycle 1 day 1 serum concentration (μg/mL)			Cycle 3 day 1 serum concentration (μg/mL)		
	Mean	CV%	Individual maximum	Mean	CV%	Individual maximum
0·25 mg/kg (3 weeks; n=3)	4·42	20·13	5·40	4·95	15·63	5·65
0·75 mg/kg (3 weeks; n=3)	20·47	33·51	24·79	21·34	25·45	25·68
1·25 mg/kg (3 weeks; n=3)	26·71	27·95	35·07	26·21	18·59	29·65
3·75 mg/kg (3 weeks; n=27)	72·88	20·06	113·17	82·69	24·37	120·67
3·75 mg/kg (2 weeks; n=16)	77·23	14·35	101·25	86·97	14·50	108·46

CV%=coefficient of variation.

Table 3: **Serum concentration of MABp1 by dose level**

There were proportionally fewer CD14 and CD16, positive monocytes that were also positive for interleukin-1α after treatment (cycle 2, day 15; mean 45% [SD 24]) compared with baseline (57% [25]); however, this difference was not significant (p=0·62; figure 2A). The proportion of monocytes positive for CD14, CD16 and interleukin-1α seemed to rebound during cycle 1 as serum concentrations of MABp1 decreased (figure 2A).

Platelet counts revealed increases between baseline and week 8 at doses of 0·25 mg/kg, 0·75 mg/kg, and 1·25 mg/kg (figure 2B). The platelet counts in patients given MABp1 at 3·75 mg/kg every 3 weeks (n=27) and

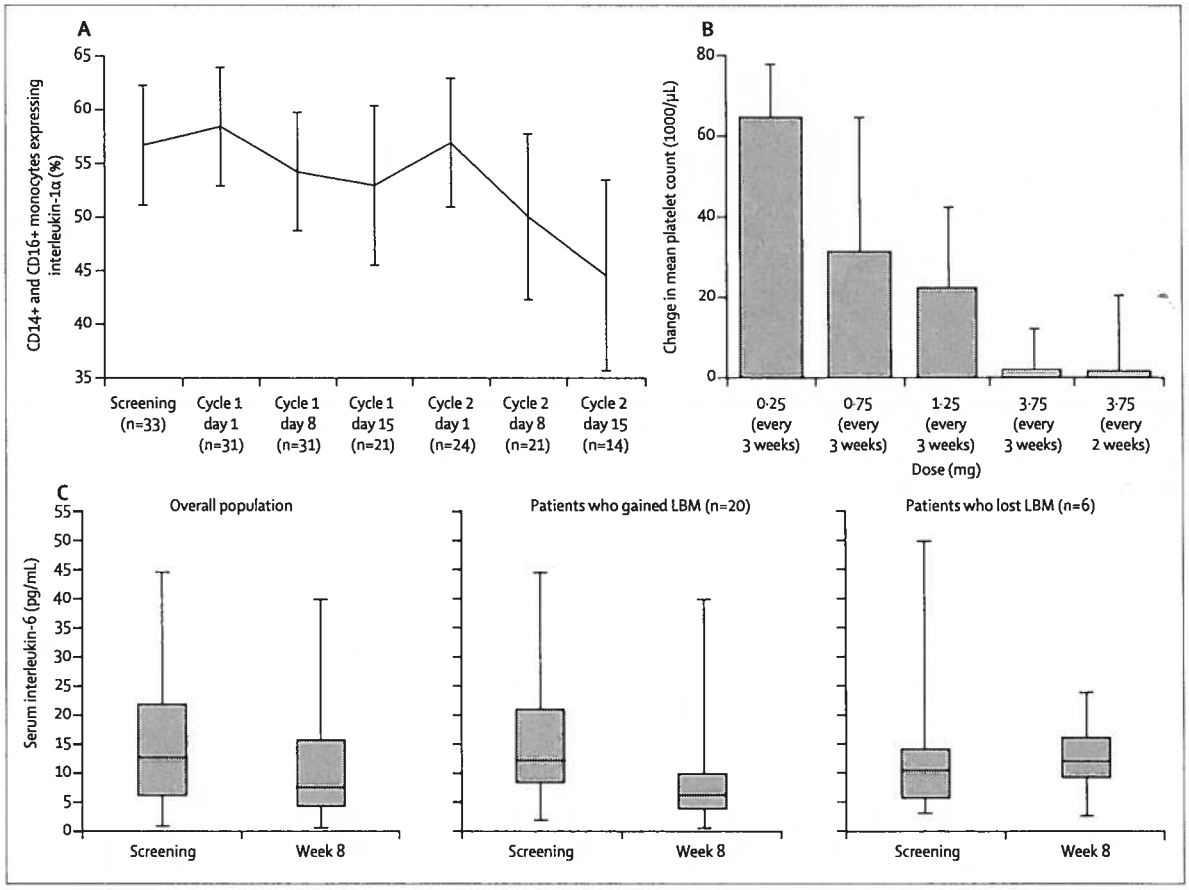

Figure 2: **Pharmacodynamic effects of MABp1**

(A) Presence of interleukin-1α-expressing monocytes in peripheral blood as a percentage of CD14 and CD16 positive monocytes. (B) Change in mean platelet count between baseline and week 8 (after four rounds of antibody therapy). (C). Plasma interleukin-6 concentrations for the overall population and for patients who lost or gained LBM. The box depicts the median and IQR, and the whiskers depict the range. LBM=lean body mass.

every 2 weeks (n=16) remained stable (equivalence test p<0·0001 for both cohorts).

In 42 patients, median plasma interleukin-6 concentrations were 12·8 (IQR 6·6–27·7) at baseline compared with 7·6 (4·5–15·7) at week 8 (median change –2·7; IQR –12·6 to 3·0, p=0·08, Wilcoxon signed-rank test, figure 2C). Mean changes are shown in the appendix.

See Online for appendix

30 patients completed baseline and week 8 DEXA scans. Lean body mass increased by a mean of 1·02 kg (SD 2·24, 95% CI 0·21–1·82; p=0·02). 21 of these patients (70%) showed an increase in lean body mass after three infusions (mean 1·92 kg [SD 1·99], 95% CI 1·08–2·77; p<0·0001) at the week 8 DEXA assessment (figure 3). Total bodyweight changed by a mean of 0·94% (SD 3·34; 95% CI –0·5 to 2·4) in those who gained lean body mass and by a mean of –0·89% (3·98; –2·3 to 1·7) in those who lost lean body mass. Weight loss was not an entry criterion for this trial; however, a post-hoc chart review of patients with lean body mass data revealed that 23 (77%) of 30 patients were losing weight in the 6 months before enrolment. In patients who gained lean body mass, fat mass changed by a median of –4·4% (IQR –10·7 to 0·8), and in those who lost lean body mass, it changed by –2·5% (–6·7 to 0·9). Compared with baseline, median energy expenditures were reduced at week 8 (median –35 kcal per day; IQR –105 to 275) for patients who had increased lean body mass, but were increased in those who had reduced lean body mass (median 135 kcal per day, IQR –105 to 275). In the overall population, median energy expenditure increased by 12·79 kcal/day (IQR 6·93–24·99).

Of the 21 patients with an increase in lean body mass, one patient with Castleman's disease had extremely high interleukin-6 concentrations (baseline 3500 pg/mL) and was excluded from further exploratory analyses. In the 20 patients who gained lean body mass and for whom interleukin-6 plasma measures were available, an exploratory analysis showed that plasma interleukin-6 concentrations decreased significantly between baseline and week 8 (median 12·3 pg/mL, IQR 8·5–21·1 *vs* 6·2 pg/mL; 3·9–9·9; median change –3·2, –13·8 to 1·2; p=0·042), whereas for the six patients who lost lean body mass, there was no difference in plasma interleukin-6 concentration (median 10·6 pg/mL,

IQR 5·8–14·2 *vs* 12·2 pg/mL, 9·4–16·2; median difference 0·4, –0·6 to 7·5; p=0·91; figure 2C).

In the overall patient population, baseline mean and median C-reactive protein concentrations were 419 nmol/L (SD 507) and 195 nmol/L (IQR 33–556), respectively; however, the variation (range 0–2171 nmol/L) was substantial. Among patients with baseline concentrations greater than 29 nmol/L, a non-significant reduction was noted at week 8 (data not shown; p=0·76).

EORTC-QLQ C30 assessments at baseline and week 8 were available for 33 patients for all subscales except appetite, for which the follow-up response was missing for one patient. Compared with baseline, significant improvements were reported on day 1 of cycle 3 in social (p=0·042), emotional (p=0·032), and role function scores (p=0·0062; figure 4; appendix). Decreases in fatigue (p=0·0084), pain (p=0·025), and appetite loss (p=0·020) were also noted. At baseline, 15 patients reported some level of appetite loss, whereas 17 had normal appetite. At follow-up, 11 of 15 patients (73%, 95% CI 64–82) experienced an improvement in appetite. Of the patients with no appetite loss at baseline, 14 of 17 (82%, 95% CI 74–90) maintained their normal appetite. Patients reported a significant improvement in global quality-of-life score, from 4·8 to 5·4 (mean change 0·6, 95% CI 0·1–1·2; p=0·021).

42 patients were eligible for restaging using RECIST. 18 patients experienced clinical progression before 8 weeks and refused radiographic restaging. 20 patients were restaged at 8 weeks. Additionally, four patients who progressed before this timepoint had radiographic restaging data available and were included in the response analysis. Nine of these 24 patients had stable disease or better for at least 3 months (stable disease in eight; partial response in one); of these nine, five remained on trial for over 6 months and three for over 12 months (table 4). The partial response was in a patient with refractory *KRAS*-mutant colorectal cancer who was on study for 72 weeks. Ten patients with NSCLC were restaged using the ir-RC at 10 weeks, two of whom had stable disease (16 weeks and 18 weeks).

Radiographic evidence of tumour shrinkage was noted in some patients. A patient with NSCLC who had pulmonary lesions after three doses of MABp1 underwent cavitation and showed significant loss of metabolic activity as assessed by ^{18}F-fluorodeoxyglucose-PET. A patient with multifocal Castleman's-associated POEMS syndrome showed a substantial reduction of plasma interleukin-6 concentrations. This patient had debilitating and aggressive disease and had previously failed anti-interleukin-6 monoclonal antibody treatment. With MABp1 treatment, serum interleukin-6 concentrations decreased from 3500 pg/mL at baseline to 1800 pg/mL by week 8, with a continued decrease to 2 pg/mL at week 59. This pharmacodynamic response was associated with durable standard and symptomatic improvement for 31 months.

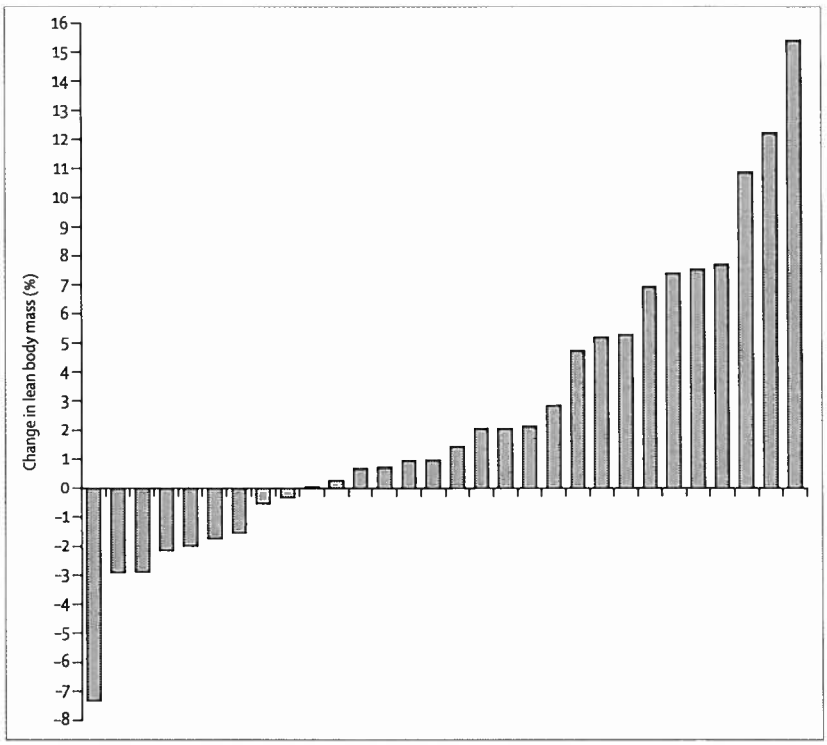

Figure 3: **Change in lean body mass between baseline and week 8**
Each bar represents the change in lean body mass for one patient.

18 different tumour types were treated in this study. Therefore, meaningful analysis of survival for patients with infrequent tumours in this study could not be done. However, in a post-hoc analysis, patients with colorectal cancer (n=14) were assessed for overall survival. The median overall survival for these patients was 8·7 months (IQR 6·4–22·1). However, in a post-hoc exploratory analysis, survival outcomes in patients with colorectal cancer who had increases in lean body mass showed numerically longer survival than those who lost lean body mass during the study (median 19·3 months *vs* 6·6 months), but this finding was not significant (log-rank p=0·098; appendix). Patients with NSCLC were also assessed for overall survival; these findings will be presented in a separate report.

Discussion

To our knowledge, MABp1 is the first therapy to specifically target interleukin-1α, and the first of a new generation of true human monoclonal antibodies (panel). The absence of any reported infusion reactions or detectable anti-drug neutralising responses even after treatment for more than 2 years suggests that this treatment is safe. The most common possibly related adverse events were proteinuria, nausea, and fatigue. Biological activity was suggested by disease control in some patients, increases in lean body mass in some

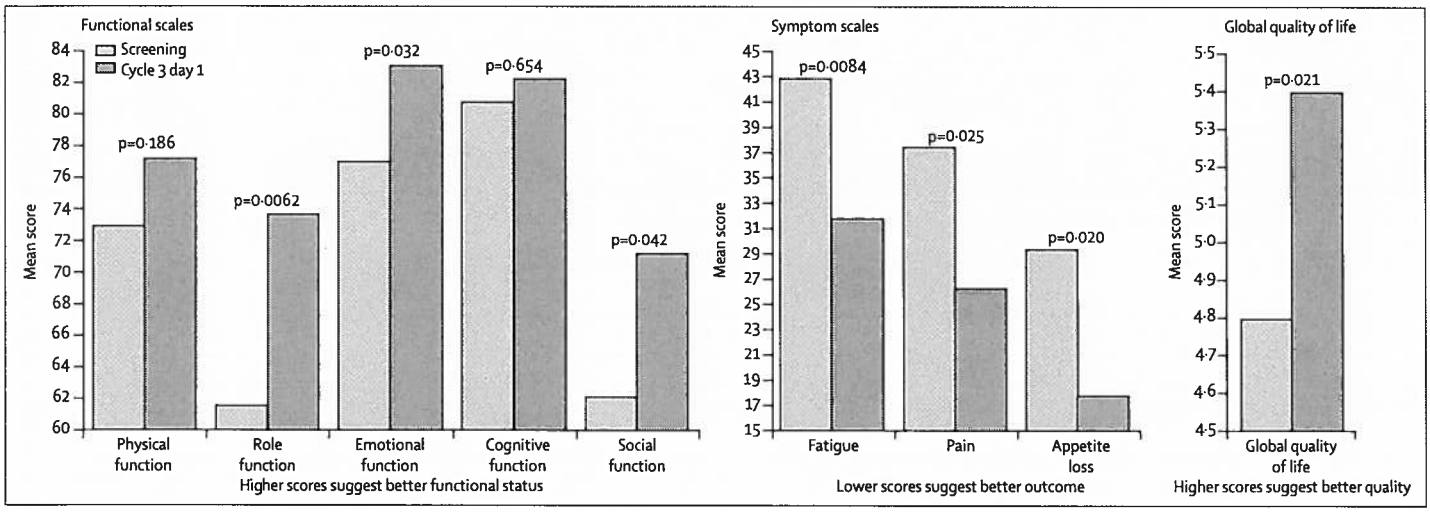

Figure 4: **Change in quality of life as assessed by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire**

	Tumour assessment method	Tumour type	Dose (mg/kg)	Dose frequency (weeks)	Best response	Weeks on study
Patient 3	RECIST	Renal cell	0·25	3	SD	12
Patient 4	RECIST	Colorectal	0·75	3	PR	72
Patient 5	RECIST	Castleman's	3·75	3	SD	128
Patient 6	RECIST	NSCLC	1·25	3	SD	15
Patient 15	RECIST	NSCLC	3·75	3	SD	45
Patient 16	RECIST	Rectal	3·75	3	SD	18
Patient 27	RECIST	Neuroendocrine	3·75	3	SD	45
Patient 36	RECIST	Pseudomyxoma	3·75	3	SD	121
Patient 56	RECIST	NSCLC	3·75	3	SD	12
Patient 74	irRC	NSCLC	3·75	2	SD	16
Patient 76	irRC	NSCLC	3·75	2	SD	18

irRC=Immune Related Response Criteria. NSCLC=non-small-cell lung cancer. PR=partial response. RECIST=Response Evaluation Criteria in Solid Tumours. SD=stable disease.

Table 4: **Patient responses according to tumour type and dose**

patients, and decreases in fatigue, pain, and appetite loss. In our opinion, although not statistically significant, it was also was suggested by evidence of a decrease in interleukin-6 concentrations.

Positive and negative selection of antibody-producing cells is a cornerstone of adaptive immunity; thus, affinity-matured antibodies against autoantigens, such as interleukin-1α, were not anticipated by immunologists. Because we were able to isolate this antibody from an individual, this finding suggests that affinity-matured antibodies do exist against self-antigens. Clinical evidence from this study supports preclinical data that implicate these antibodies as being important in immunoregulatory functions. The safety and tolerability reported in this study points to the potential safety and tolerability of true human antibodies as next-generation antibody therapeutics.

The anti-interleukin-1α treatment was used in an attempt to block chronic inflammation underlying the malignant phenotype.[2,4,5] Since no meaningful concentrations of interleukin-1α are detectable in serum, the primary target for interleukin-1α was expected to be expressed on the surface of platelets, monocytes expressing CD14 and CD16, and malignant cells.[26–29] Although the antibody therapy targets leucocytes and platelets,[30] there was no treatment-related depletion of peripheral blood cells.

We saw a decrease in proportion of cells staining positive for interleukin-1α, CD14, and CD16 between baseline and after treatment. This finding could have resulted from steric competition for interleukin-1α binding with the staining reagent, since the absolute number of monocytes did not decline. Although the change was not significant, rebounding of interleukin-1α positive, CD14 positive, and CD16 positive monocytes with waning serum concentrations of MABp1 suggests interleukin-1α was targeted on these monocytes by treatment.

Interleukin-1 induces interleukin-6 production in vitro and in animal models,[31] but, to our knowledge, this is the first clinical evidence that interleukin-6 concentrations in humans can be controlled by neutralisation of interleukin-1α. This effect was dramatic in a patient with Castleman's disease, whose serum interleukin-6 concentrations declined from 3500 pg/mL at baseline to 2 pg/mL at week 59. In our opinion, although not statistically significant, the fact that there was evidence of a decrease in interleukin-6 concentrations between baseline and week 8, which seemed to be associated with lean body mass response, suggests that interleukin-6 might be a better pharmacodynamic marker of interleukin-1 antagonism than C-reactive protein. The variation in C-reactive protein concentration was substantial, which is probably a result of the many types of tumours included in the trial.

Systemic chronic inflammation, serum interleukin-6 concentrations, and disease progression seem to be inter-related. Patients who had increased lean body mass had numerically greater reductions in interleukin-6 concentrations than the overall population, although only a small number of patients were included in this exploratory analysis. The potential for interleukin-6 to directly mediate cachexia has been reported in both preclinical and clinical investigations, and improved outcomes in patients with respect to lean body mass or other measures could be caused in part by a reduction in systemic interleukin-6 concentrations.[32,33]

Anti-interleukin-1α therapy was not expected to be directly cytotoxic to tumours. However, anti-tumour activity was noted in some cases. Tumour regression in the setting of a *KRAS* mutation is interesting in view of reports that suggested a mechanistic link between interleukin-1α signalling and progression of *KRAS*-positive tumours.[34,35] Although how interleukin-1α antagonism might facilitate regression of established tumours is not yet fully understood, the antitumour effect might be more fully recognised by criteria other than RECIST.[36]

Inflammatory cells infiltrate the tumour microenvironment and enhance tumour viability by producing factors that stimulate the growth of microvasculature.[37] More recently, infiltrating leucocytes, particularly the so-called tumour-associated macrophages and myeloid-suppressor cells, have been understood to play a more dynamic part in tumour viability than previously realised by protecting tumours from the activity of effector cytotoxic T lymphocytes. The ability of tumour-associated macrophages and myeloid-suppressor cells to promote regulatory T lymphocytes in the tumour microenvironment represents a crucial mechanism for avoidance of clearance by the immune system.[38] Drugs targeting key molecular elements involved in control of effector cytotoxic T lymphocytes and regulatory T lymphocytes, such as cytotoxic T-lymphocyte antigen 4 and programmed cell death 1, have been used successfully as immune-modulating approaches to tumour treatment.[39] Interleukin-1α blockade using a monoclonal antibody is expected to, among other activities, produce an anti-inflammatory effect by reducing circulating leucocyte extravasation and infiltration into the tumour microenvironment. Interleukin-1α blockade might result in less infiltration of the microenvironment by tumour-associated macrophages and myeloid-suppressor cells, in turn reducing the suppression of host cytotoxic effector cytotoxic T-lymphocyte activity against the tumour. This suggestion could help explain the observed disease control.

Signalling through the interleukin-1 receptor mediates cachexia,[40,41] particularly through neuronal activation in the fenestrated microvasculature of the hypothalamus. Metabolic dysregulation as a result of chronic sterile inflammation could thus be mediated via interleukin-1α on circulating tumour cells, activated peripheral blood cells, or tumour–platelet microemboli. Patients were thus examined for lean body mass changes before and after treatment. Lean body mass gains occurred in 70% of patients analysed with DEXA. These patients gained lean body mass while losing fat tissue, suggesting a changing use of metabolic energy, with mobilisation of fat stores in favour of rebuilding muscle reserve. As far as we know, there have been no previous reports of spontaneous lean body mass increases in patients with refractory cancer. Changing utilisation of energy reserves in these patients raises the intriguing notion that anti-interleukin-1α therapy might attenuate metabolic dysregulation and facilitate physical recovery in advanced cancer.

Quality-of-life assessments using the validated EORTC-QLQ C30 were consistent with DEXA measures

***Panel:* Research in context**

Systematic review

We searched PubMed between 1990 and 2008 for studies published in English using various terms including combinations such as "interleukin 1 and cancer", "IL-1 and cachexia", "IL-1 and inflammation", and "IL-1 and fever". These searches yielded over 6000 journal articles. There were many preclinical reports that described the role of interleukin-1 or interleukin-1α in enhancement of neoplastic potential through various mechanisms, including promotion of neoangiogenesis, upregulation of matrix metalloproteinase, and activation of vascular endothelium. Also, some reports suggested a role for interleukin-1 in wasting and cachexia. The source of the interleukin-1α was specifically on tumour cells, infiltrating peripheral blood cells, and released from necrotic host cells. Many studies also linked interleukin-1α expression on human malignant tumour biopsies with a more aggressive clinical course than that for tumours with no interleukin-1α expression on biopsy. Animal experiments using mice with gene-targeted deletion of interleukin-1α also showed dramatic reduction in growth of some tumours. We then did a PubMed search, filtered for clinical trials, using the terms "IL-1" and "cancer", which resulted in 71 manuscripts. Only one trial used interleukin-1 blockade: a trial of an interleukin-1 receptor antagonist in refractory myeloid leukaemia.[22] An additional PubMed search using the terms "interleukin 1 alpha" and "cancer", and filtered for clinical trials revealed 15 trials in which interleukin-1α was administered as an investigational drug to patients with cancer. The cytokine was used as a primary therapy, a vaccine adjuvant, and as a myelostimulatory drug after chemotherapy. The results of these trials showed substantial toxicity, including hypotension, capillary leak, fever, rigors, myalgias, fatigue, oedema, thrombocytosis, and nausea and vomiting.[23,24] These effects occurred at doses as low as 0·1 μg.[25] Furthermore, there was no evidence of any antineoplastic activity. These data show that over-stimulation of the interleukin-1 system, specifically with interleukin-1α, could directly result in many of the devastating symptoms that occur in patients with advanced cancer.

Interpretation

Interleukin-1α is a potent inducer of sterile inflammation and is active at low doses. Upregulation of this activity results in tumour growth, spread, and systemic toxicities that occur in periods of acute stress (eg, trauma and infection) and in advanced cancer. In the present study, we show that MABp1, a first-in-class true human antibody, is well tolerated and is associated with biological activity including increases in lean body mass and disease control. Study limitations include small numbers for each tumour type treated and absence of a control arm. Regardless, the findings suggest an important role for interleukin-1α blockade in the treatment of patients with advanced cancer, which warrants exploration in larger studies.

overall. Results of EORTC-QLQ C30 assessments showed improvement in fatigue, appetite loss, pain, and some functional outcomes. Taken together, the apparent correction of a metabolic defect in these patients, together with improved global quality-of-life measures, suggests a reduction in a systemic inflammatory process.

Overall survival was assessed in patients with colorectal cancer. This group had a median survival of 8·7 months, which compares with historical data from similar patient populations (ranging from 4·6 to 5·0 months).[42,43] However, the limited number of patients and retrospective analysis precludes definitive conclusions.

Compared with the change in lean body mass, baseline ECOG score is a well-established prognostic parameter.[44] However, because of the limited number of patients in each category, associations between ECOG score and prognosis could not be identified. Furthermore, one of the points of the study was to treat advanced cancer by moderating chronic inflammation. C-reactive protein and interleukin-6 are well-known biomarkers of systemic inflammation, and changes in these parameters should be investigated in future studies of this molecule with more homogeneous participants. In the context of this study, the results of these assessments were heterogeneous, perhaps because of the diverse group of tumours included, making definitive conclusions more difficult to draw.

In conclusion, MABp1 was well tolerated, showed biological activity including positive effects on body composition and quality of life, and showed some antitumour activity. Even so, limitations of the study include the small number of patients and the fact that a prospective study is needed to establish that antibody therapy increases lean body mass and that this increase is a robust surrogate for a survival advantage. Therefore, two randomised controlled studies of this novel anti-inflammatory molecule in patients with colorectal cancer have been started (NCT01767857, and one study not yet registered).

Contributors

DSH contributed to study design, data collection and interpretation, writing, literature search, and figures. DHu contributed to study design, data collection and analysis, and reviewing the manuscript. EB contributed to the literature search and study design. FJ contributed to data analysis. AN contributed to data analysis and interpretation. GSF contributed to data collection, patient enrolment, and review and approving the manuscript. SP-P and SF contributed to trial conception and design, and writing, reviewing, and revising the manuscript. JJW and AMT contributed to data collection and approved the manuscript. MS and PM contributed to the literature search, data analysis and interpretation, figures, and writing the manuscript. JS contributed to study design, literature search, data analysis and interpretation, figures, and writing the manuscript. RK contributed to data analysis and interpretation, and writing the manuscript.

Declaration of interests

DSH and DHu have received grants from Xbiotech during this study. MS and PM are employees of and hold stock options for XBiotech. JS is an employee of and holds stock options for XBiotech and holds patents related to anti-interleukin-1α therapy. RK has received funding for research from XBiotech. All other authors declare that they have no competing interests.

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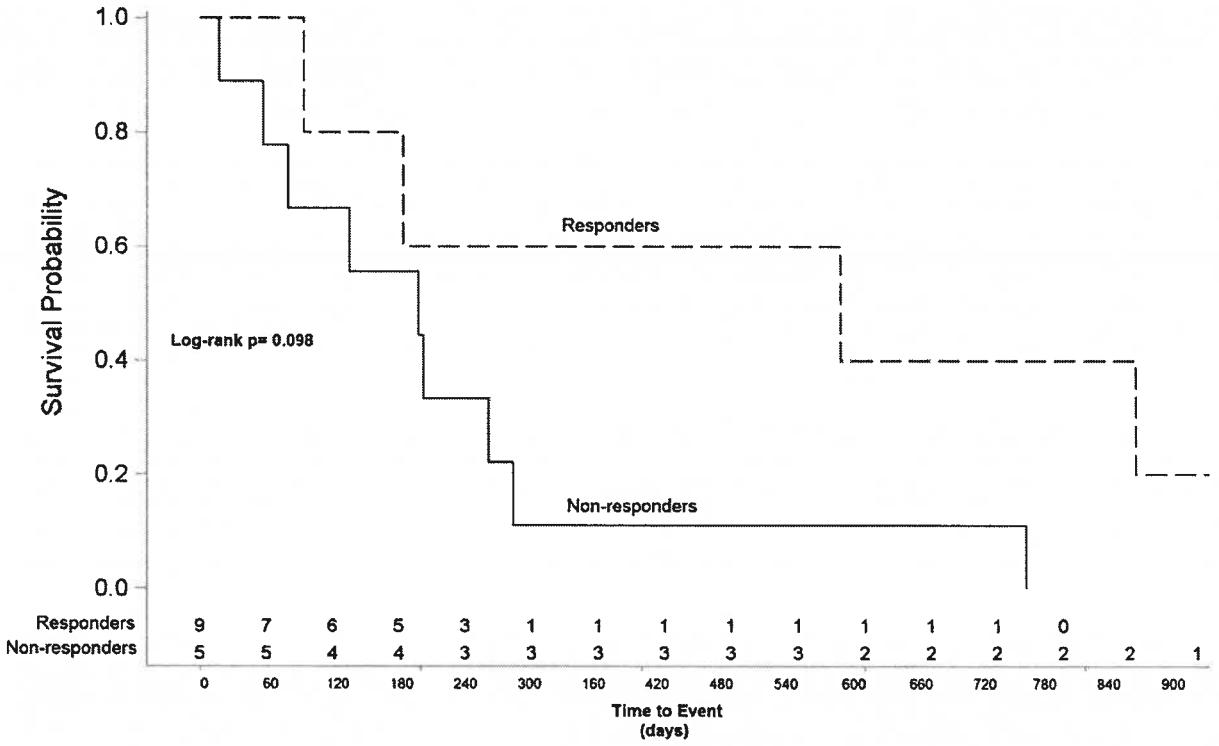
Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Hong DS, Hui D, Bruera E, et al. MABp1, a first-in-class true human antibody targeting interleukin-1α in refractory cancers: an open-label, phase 1 dose-escalation and expansion study. *Lancet Oncol* 2014; published online April 17. http://dx.doi.org/10.1016/S1470-2045(14)70155-X.

Appendix: MABp1 in Advanced Cancers



Supplemental Figure 1. Kaplan–Meier curve showing survival among colorectal cancer patients (n=14) according to evidence of LBM increase. 5 of 14 (36%) responded with an increase in LBM after just 8 weeks (3 infusions). Restaging was performed 8 weeks following commencement of therapy. Patients with LBM increase had a median overall survival of 19.3 months, while others had a median survival of 6.6 months (log rank p=0.098)

Supplemental Table 1: Change in Quality of Life scores from baseline to cycle 3 day 1, as assessed by EORTC-QLQ C-30

EORTC Scales	Baseline	Cycle 3 Day 1	Change	p value
Functional Domains				
Physical Functioning, Mean±SD	73.9±22.45	77.2±22.55	3.2±13.76	0.19
Role Functioning, Mean±SD	61.6±34.98	73.7±26.36	12.1±23.67	0.0062
Emotional Functioning, Mean±SD	77.0±23.30	83.1±16.60	6.1±15.49	0.032
Cognitive Functioning, Mean±SD	80.8±20.46	82.3±19.96	1.5±19.26	0.65
Social Functioning, Mean±SD	62.1±31.26	71.2±24.39	9.1±24.68	0.042
Symptom Domains				
Fatigue, Mean±SD	42.8±29.54	31.7±19.86	-11.1±22.74	0.0084
Pain, Mean±SD	37.4±39.97	26.3±30.63	-11.1±27.22	0.025
Appetite loss, Mean±SD	29.3±37.97	17.7±25.38	-12.5±29.02	0.022
Global Score				
Global QoL, Mean±SD	4.8±1.50	5.4±1.43	0.6±1.43	0.021

EORTC= European Organization for Research and Treatment of Cancer, QoL= Quality of Life
Functional Scores: An increase in scores indicates improved functions.
Symptoms Scores: A decrease in scores indicates a decrease in symptoms.
Global Score: An increase indicates improvement.

Supplemental Table 2: Change in plasma IL-6 level from baseline to week 8

	Baseline	Week 8	Change	p value
Over all (n=42), Mean±SD (median, IQR), pg/ml	20.8±23.4 (12.8, 6.2 to 21.9)	15.9±27.1 (7.6, 4.5 to 15.7)	-4.9±26.7 (-2.7, -12.6 to 3.0)	0.081
Responders (n=20), Mean±SD (median, IQR), pg/ml	16.5±12.5 (12.3, 8.5 to 21.1)	10.9±12.9 (6.2, 3.9 to 9.9)	-5.6±13.4 (-3.2, -13.2 to 1.2)	0.042
Non-responder (n=9), Mean±SD (median, IQR), pg/ml	16.9±22.6 (10.6, 5.8 to 14.2)	13.0±6.3 (12.2, 9.4 to 16.2)	-3.8±20.6 (-0.4, -3.6 to 7.5)	0.91

IQR= inter quartile range, IL-6= Interleukin 6