Phase I study of imalumab (BAX69), a fully human recombinant antioxidized macrophage migration inhibitory factor antibody in advanced solid tumours

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Aim: Preclinical evidence suggests that oxidized macrophage migration inhibitory factor (oxMIF) may be involved in carcinogenesis. This phase 1 study (NCT01765790) assessed the safety, tolerability, pharmacokinetics and antitumour activity of imalumab, an oxMIF inhibitor, in patients with advanced cancer using ‘3 + 3’ dose escalation.

Methods: In Schedule 1, patients with solid tumours received doses from 1 to 50 mg/kg IV every 2 weeks. In Schedule 2, patients with metastatic colorectal adenocarcinoma, non-small-cell lung, or ovarian cancer received weekly doses of 10 or 25 mg/kg IV (1 cycle = 28 days). Treatment continued until disease progression, unacceptable toxicity, dose-limiting toxicity, or withdrawal of consent.

Results: Fifty of 68 enrolled patients received imalumab. The most common treatment-related adverse events (TRAEs) included fatigue (10%) and vomiting (6%); four grade 3 serious TRAEs (two patients) occurred. The dose-limiting toxicity was...
Conclusions: Imalumab had a maximum tolerated dose of 37.5 mg/kg every 2 weeks in patients with advanced solid tumours, with a biologically active dose of 10 mg/kg weekly. Further investigation will help define the role of oxMIF as a cancer treatment target.

KEYWORDS
clinical trials, pharmacokinetics, phase I

1 | INTRODUCTION

Macrophage migration inhibitory factor (MIF) is a pleiotropic, pro-inflammatory cytokine that plays a key role in regulating innate immunity, especially macrophage function and differentiation.1,2 It is widely and constitutively expressed by immune and nonimmune cells, and is also present in the circulation of healthy individuals.3,4 MIF has been implicated in the pathogenesis of several inflammatory diseases5,6 and tumour growth promotion.3,6 Compared with healthy people, patients with cancer can have higher levels of circulating MIF and overexpression of MIF in tumour tissue, which have been associated with high tumour burden and grade, increased metastasis risk and poor prognosis.7-12 Neutralizing anti-MIF antibodies inhibited tumour growth and angiogenesis in animal models of B cell lymphoma,13 prostate cancer14 and colon cancer.15

MIF occurs in two conformational isoforms: oxidized MIF (oxMIF) and reduced MIF (redMIF).5 RedMIF is predominantly detected in plasma from healthy individuals,5 whereas oxMIF is detected in patients with acute and chronic inflammatory diseases or solid tumours.5,16 MIF oxidation has been reported by several groups, with modifications occurring at different sites resulting in functional implications including loss of tautomerase activity (inhibiting pro-inflammatory activities of MIF), interference with CD74 binding (preventing signalling and co-activation of CD44), association with disease, regulation of activated B and T cells, increased cardioprotective properties, and decreased activation of ERK1/2 and AKT signalling.17 OxMIF is specifically expressed in tumour types including colorectal carcinoma (CRC), non-small cell lung cancer (NSCLC) and ovarian cancer.16

Imalumab (BAX69) is a recombinant, fully human, monoclonal antibody that binds specifically to oxMIF.5 It is specific for a b-sheet structure within MIF including a highly conserved catalytic motif (57Cys-Ala-Leu-Cys60) of the thiol protein oxidoreductase, which is linked to the biologic function of MIF.4,18,19 In preclinical studies, imalumab and two similar, specific anti-oxMIF antibodies were shown to interfere with key signalling pathways involved in cell survival and proliferation.16,20 These antibodies inhibited MIF-induced phosphorylation of ERK1/2 and AKT, promoted apoptosis through activation of caspase-3 in prostate cancer cells and led to inhibition of PC3 xenografts in a dose-dependent manner.20 Additionally, they sensitized prostate and ovarian cancer cell lines to cytotoxic drugs.16

Here, we report results from the first-in-human phase I study to assess the safety, dose-limiting toxicity (DLT), maximum tolerated dose (MTD), pharmacokinetics, pharmacodynamics and antitumour activity of imalumab in patients with advanced solid tumours.

2 | METHODS

2.1 | Patient population

Patients were included if they were aged ≥18 years; had an anticipated life expectancy of >3 months at screening; histologically confirmed malignant solid tumour (Schedule 1) or histologically or
cytologically confirmed metastatic CRC (mCRC), NSCLC (mNSCLC), or ovarian cancer (Schedule 2); had refractory tumours, or had progressed on, were considered medically unsuitable for, or refused standard of care treatment; had measurable or evaluable disease, defined by Response Evaluation Criteria in Solid Tumors (RECIST v1.1; had an Eastern Cooperative Oncology Group (ECOG) performance status ≤1; had adequate haematological, renal, and liver function; and (for Schedule 2) had a tumour amenable to biopsy and willingness to undergo a biopsy before and at least once after treatment.

Key exclusion criteria were known brain tumours or central nervous system metastases; uncontrolled hypertension or clinically significant cardiovascular disease; any antitumour therapy within 4 weeks (6 weeks for nitrosoureas, mitomycin C) before starting imalumab; and previous treatment-related toxicity not recovered to ≤ grade 2 (according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v4.03).

Patients provided informed consent before entering into the study (ClinicalTrials.gov identifier: NCT01765790). The study was conducted in accordance with the International Conference on Harmonization Guideline for Good Clinical Practice E6 (April 1996), Title 21 of the US Code of Federal Regulations, the European Clinical Trial Directive (2001/20/EC and 2005/28/EC), and applicable national and local regulatory requirements. The study was approved by the relevant ethics committees.

2.2 | Study design and treatment

This was a multicentre, open-label, dose-escalation phase I study evaluating two schedules of imalumab using a classic ‘3 + 3’ design in Schedule 1 (Supporting Information Figure S1). The study initiated with Schedule 1 to assess the safety, pharmacokinetic and pharmacodynamic endpoints in patients with malignant solid tumours receiving the study drug every 2 weeks (Q2W). Schedule 2 started after Schedule 1 completion to evaluate a weekly (QW) dose escalation in patients with mCRC, mNSCLC and metastatic ovarian cancer refractory to or failing standard treatments (platinum-free interval and platinum resistance were not considered for metastatic ovarian cancer). This schedule was designed based on results of early pharmacokinetic analyses in Schedule 1, which indicated that imalumab had a shorter than expected half-life (t1/2). The typical t1/2 of Immunoglobulin G (IgG)-derived molecules such as imalumab is 2-3 weeks.21

In Schedule 1, imalumab was administered intravenously every 2 weeks (days 1 and 15) at escalating planned dose levels of 1, 3, 10, 25, 37.5 and 50 mg/kg body weight. The starting dose of 1 mg/kg represents a 25-fold safety factor versus the repeated dose no-observed-adverse-effect-level of 25 mg/kg in cynomolgus monkeys from nonclinical studies. In Schedule 2, imalumab was administered intravenously QW (days 1, 8, 15 and 22) at planned dose levels of 10, 25 and 37.5 mg/kg body weight. In Schedule 2, an expansion cohort (Supporting Information Figure S1) was planned to enrol up to 24 additional patients with mCRC, mNSCLC and metastatic ovarian cancer (eight or fewer patients per tumour type) treated at or below the MTD for this schedule. Cycles were repeated every 28 days until disease progression, unacceptable toxicity, DLT or consent withdrawal.

The primary objective was to determine the safety and tolerability of imalumab, including the MTD and immunogenicity, in patients with malignant solid tumours (Schedule 1) and in patients with mCRC, mNSCLC or metastatic ovarian cancer (Schedule 2). Secondary objectives were to determine the pharmacokinetics of imalumab, explore pharmacodynamic markers indicative of antitumour and anti-MIF activity, explore tissue penetration and target binding of imalumab in tumour tissue, and to assess the antitumour activity of imalumab, if any.

2.3 | Safety assessments

NCI CTCAE v4.03 criteria were used to assess the severity of adverse effects (AEs) and their causal relationship to imalumab. DLT was defined as any treatment-emergent ≥ grade 3 nonhematologic toxicity, grade 4 hematologic toxicity, grade 3 febrile neutropenia, or grade 3 thrombocytopenia associated with bleeding. MTD was defined as the highest dose level examined at which less than one-third of evaluable patients experienced a DLT during the first treatment cycle.

2.4 | Assessments of immunoglobulin against imalumab

Plasma samples obtained at baseline and after exposure were tested for the presence of total immunoglobulin against imalumab (binding antibodies) using an internally validated homogeneous bridging electrochemiluminescence assay (IPM Biotech GmbH [now part of Bioagilytix Europe GmbH] Hamburg, Germany). Samples with confirmed positive antibodies were analysed for the presence of neutralizing antibodies against imalumab using an internally validated competitive ligand binding assay (IPM Biotech GmbH).

2.5 | Pharmacokinetics and pharmacodynamics

Blood samples to determine the pharmacokinetics of imalumab and the measurement of circulating oxMIF (oxMIF ± bound imalumab) and circulating total MIF levels were collected in Schedule 1 at baseline; in cycle 1, pre and post infusion on day 1 and at 1, 4, 8, 24, 72 and 168 hours after infusion, as well as pre infusion on day 15; in cycle 2, pre infusion on day 1, pre and post infusion on day 15, and at 1, 4, 8, 24, 72 and 168 hours after infusion; pre infusion on day 1 of all subsequent cycles; and at the end of treatment.

In Schedule 2, blood samples were collected at baseline; in cycle 1, pre infusion on days 1, 8, 15 and 22, as well as immediately post infusion on day 1 and at 1, 4, 8, 24 and 72 hours after this infusion; in cycle 2, pre infusion on days 1, 8, 15 and 22, and post infusion on day 15, and at 1, 4, 8, 24 and 72 hours after this infusion; pre infusion on day 1 of all subsequent cycles; and at the end of treatment.
Imalumab concentration was determined by a specific anti-MIF enzyme-linked immunosorbent assay. Briefly, imalumab was captured by precoated MIF and detected after blocking and washing steps by a rabbit antihuman IgG peroxidase conjugate. Imalumab was quantified against an internal reference standard.

Details regarding precision, accuracy and sensitivity of the assays used in both schedules are included in the Supporting Information data S1.

Pharmacodynamic markers indicative of imalumab antitumour and anti-MIF activities were explored by assessing tumour response, tissue penetration and target occupancy. Imalumab tissue penetration and target occupancy were investigated in patients from Schedule 2 by analysing levels of circulating oxMIF, circulating total MIF and imalumab in tumour tissue from metastatic lesions obtained pre and post treatment. Biopsies were embedded in optimal cutting temperature compound and frozen, transferred to and distributed by Quest Diagnostics (Madison, New Jersey) and cryosectioned by BioQuant (Heidelberg, Germany). Separate, consecutive tissue sections from tumour biopsies were stained for imalumab and oxMIF by immunohistochemistry at Baxalta Innovations GmbH (a Takeda company, Vienna, Austria). Details of pathological review and digital image analyses are summarized in the Supporting Information data S1.

Tumour measurement was assessed at baseline, on cycle 2, day 28, at the end of every subsequent even-numbered cycle thereafter, and at the end of the study, with tumour response assessed by investigators using RECIST v1.1.

### 2.6 Statistical analysis

The enrolled analysis set included all enrolled patients, the safety population comprised all patients who received ≥1 dose of imalumab and

![Diagram](image-url)
the full analysis dataset included all patients who received ≥1 dose of imalumab and had pharmacodynamic data at baseline and at least one time point after treatment. The pharmacokinetic analysis dataset included all patients who received at least one scheduled dose of imalumab and provided one or more evaluable post-dose concentration (ie, concentration above the lower limit of quantitation of the assay).

Best overall response (assessed using RECIST v1.1) was summarized by treatment group. Plasma concentrations of imalumab, oxMIF and total MIF and pharmacokinetic parameters were summarized using descriptive statistics. Individual subject concentration-time data were graphically presented by treatment group on linear and semilogarithmic scales.

All data processing, analyses and summaries used SAS® software package (Version 9.3 or higher). Pharmacokinetic parameters were derived using noncompartmental methods with Phoenix® WinNonlin® Version 6.4 (Certara L.P., Princeton, NJ, USA) or SAS® Version 9.2, or higher (SAS Institute, Inc., Cary, NC, USA).

3 | RESULTS

3.1 | Patients and treatment

From June 2012 to August 2016, 68 patients were enrolled: 50 patients received at least one dose of imalumab and were included in the full analysis dataset. The pharmacokinetic analysis dataset included all patients who received at least one scheduled dose of imalumab and provided one or more evaluable post-dose concentration (ie, concentration above the lower limit of quantitation of the assay).

**TABLE 1** Patient demographics and baseline characteristics

| Characteristic                  | All patients (n = 50)* |
|--------------------------------|-----------------------|
| Median age, years (range)      | 61.5 (40–87)          |
| Gender, n (%)                  |                       |
| Male                           | 23 (46)               |
| Female                         | 27 (54)               |
| Race, n (%)                    |                       |
| Caucasian                      | 45 (90)               |
| African American               | 4 (8)                 |
| Multiple                       | 1 (2)                 |
| Ethnicity, n (%)               |                       |
| Hispanic/Latino                | 12 (24)               |
| Not Hispanic/Latino            | 38 (76)               |
| Median weight, kg (range)      | 73.75 (45.9–158.6)    |
| Median BMI, kg/m² (range)      | 25.82 (17.4–49.0)     |
| Schedule 1                     |                       |
|                                | 1 mg/kg Q2W (n = 3)   |
|                                | 3 mg/kg Q2W (n = 3)   |
|                                | 10 mg/kg Q2W (n = 3)  |
|                                | 25 mg/kg Q2W (n = 6)  |
|                                | 37.5 mg/kg Q2W (n = 3)|
|                                | 50 mg/kg Q2W (n = 1)  |
| All patients (N = 50)          |                       |
| Schedule 2                     |                       |
|                                | 10 mg/kg QW (n = 28)  |
|                                | 25 mg/kg QW (n = 3)   |
|                                | 1 mg/kg Q2W (n = 3)   |
|                                | 3 mg/kg Q2W (n = 3)   |
|                                | 10 mg/kg Q2W (n = 3)  |
|                                | 25 mg/kg Q2W (n = 6)  |
|                                | 37.5 mg/kg Q2W (n = 3)|
|                                | 50 mg/kg Q2W (n = 1)  |
| ECOG performance status, n (%) |                       |
| 0                              | 2 (67) 3 (100) 0 3 (50) 2 (67) 1 (100) 11 (39) 2 (67) 24 (48) |
| 1                              | 1 (33) 0 3 (100) 3 (50) 1 (33) 0 17 (61) 1 (33) 26 (52) |
| Primary diagnosis, n (%)       |                       |
| CRC                            | 2 (67) 0 1 (33) 1 (17) 3 (100) 1 (100) 14 (50) 3 (100) 25 (50) |
| NSCLC                          | 1 (33) 0 0 0 0 0 6 (21) 0 7 (14) |
| Ovarian carcinoma              | 0 1 (33) 0 1 (17) 0 0 8 (29) 0 10 (20) |
| Other                          | 0 2 (67) 2 (67) 4 (67) 0 0 0 0 8 (16) |
| Number of prior chemotherapy regimens, n (%) |               |
| <3                             | 0 0 0 0 1 (33) 1 (100) 0 6 (21) 0 8 (16) |
| ≥3                             | 3 (100) 3 (100) 3 (100) 6 (100) 2 (67) 0 22 (79) 3 (100) 42 (84) |
| Number of prior radiotherapy treatments, n (%) |         |
| 1                              | 1 (33) 0 2 (67) 2 (33) 1 (33) 1 (100) 9 (32) 1 (33) 17 (34) |
| 2                              | 0 1 (33) 0 0 0 0 4 (14) 0 5 (10) |

**Abbreviations:** BMI, body mass index; CRC, colorectal carcinoma; ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; Q2W, every 2 weeks; QW, weekly.

*Due to the small treatment groups of this study, patient baseline demographic data that contain multiple indirect identifiers have been grouped to preserve patient anonymity.
### TABLE 2  Treatment-emergent, treatment-related adverse events

| AE, n (%) | Schedule 1 | Schedule 2 | All patients |
|-----------|------------|------------|--------------|
|          | 1 mg/kg Q2W | 3 mg/kg Q2W | 10 mg/kg Q2W | 25 mg/kg Q2W | 37.5 mg/kg Q2W | 50 mg/kg Q2W | 10 mg/kg QW | 25 mg/kg QW | All patients |
|          | (n = 3)     | (n = 3)    | (n = 6)       | (n = 3)       | (n = 1)a        | (n = 6)       | (n = 28)    | (n = 3)       | (N = 50)     |
| Grades   | All 3-5    | All 3-5    | All 3-5      | All 3-5      | All 3-5        | All 3-5      | All 3-5    | All 3-5      | All 3-5      |
| Any\(^2\) | 3 (100) 0 | 2 (67) 0 | 1 (33) 0 | 1 (17) 0 | 1 (33) 0 | 1 (100) 1 (100)a | 1 (4) 0 | 1 (4) 0 | 15 (30) 2 (4)a |
| Fatigue  | 2 (67) 0  | 0 0 0 | 1 (33) 0 | 0 0 | 1 (33) 0 | 0 | 2 (7) 1 (4)a | 0 0 | 3 (6) 1 (2)a |
| Vomiting | 1 (33) 0  | 0 0 0 | 0 0 | 0 0 | 0 0 | 0 | 1 (4) 1 (4)a | 0 0 | 2 (4) 1 (2)a |
| Constipation | 0 0 0 | 0 0 | 0 0 | 0 0 | 0 0 | 0 | 2 (7) 1 (4)a | 0 0 | 2 (4) 0 |
| Dyseusa  | 1 (33) 0  | 1 (33) 0 | 0 0 | 0 0 | 0 0 | 0 | 0 | 0 | 2 (4) 1 (2)a |
| Nausea   | 1 (33) 0  | 0 0 0 | 0 0 | 0 0 | 0 0 | 0 | 1 (4) 1 (4)a | 0 0 | 2 (4) 1 (2)a |
| Rash     | 1 (33) 0  | 1 (33) 0 | 0 0 | 0 0 | 0 0 | 0 | 0 | 0 | 2 (4) 0 |
| Allergic alveolitis | 0 0 0 | 0 0 | 0 0 | 0 0 | 0 0 | 0 | 1 (100)c | 1 (100)c | 0 0 1 (2) 1 (2)a |
| Arthralgia | 0 0 0 | 0 0 | 0 0 | 0 0 | 0 0 | 0 | 1 (4) 0 0 | 0 | 1 (2) 0 |
| Chills   | 0 0 0 | 0 0 | 0 0 | 0 0 | 0 0 | 1 (100) | 0 0 | 0 0 | 1 (2) 0 |
| Decreased appetite | 0 0 0 | 0 0 | 0 0 | 0 0 | 0 0 | 0 | 1 (4) 0 0 | 0 | 1 (2) 0 |
| Diarrhoea | 0 0 0 | 0 0 | 0 0 | 0 0 | 0 0 | 0 | 1 (4) 0 0 | 0 | 1 (2) 0 |
| Oedema peripheral | 0 0 0 | 0 0 | 0 0 | 0 0 | 0 0 | 1(33) 0 | 0 0 | 0 0 | 1 (2) 0 |
| Headache | 0 0 0 | 0 0 | 0 0 | 0 0 | 0 0 | 1 (100) | 0 0 | 0 0 | 1 (2) 0 |
| Infusion-related reaction | 0 0 0 | 0 0 | 0 0 | 0 0 | 0 0 | 1 (100) | 0 0 | 0 0 | 1 (2) 0 |
| Mental impairment | 0 0 0 | 0 0 | 0 0 | 1 (17) 0 | 0 0 | 0 0 | 0 0 | 1 (2) 0 |
| Mucosal inflammation | 0 0 0 | 0 0 | 0 0 | 0 0 | 0 0 | 0 0 | 1 (100) | 0 0 | 1 (2) 0 |
| Night sweats | 0 0 0 | 0 0 | 0 0 | 0 0 | 0 0 | 0 | 1 (4) 0 0 | 0 | 1 (2) 0 |
| Proctalgia | 0 0 0 | 0 0 | 0 0 | 0 0 | 0 0 | 0 | 1 (4) 0 0 | 0 | 1 (2) 0 |
| Pruritus | 0 0 0 | 0 0 | 0 0 | 0 0 | 0 0 | 1 (100) | 0 0 | 0 0 | 1 (2) 0 |
| Pyrexia | 0 0 0 | 0 0 | 0 0 | 0 0 | 0 0 | 0 | 1 (4) 0 0 | 0 | 1 (2) 0 |
| Urticaria | 0 0 0 | 0 0 | 0 0 | 0 0 | 0 0 | 1 (100) | 0 0 | 0 0 | 1 (2) 0 |

Abbreviations: AE, adverse event; DLT, dose-limiting toxicity; G, grade; Q2W, every 2 weeks; QW, weekly.

\(^{a}\)AE rated grade 3; there were no treatment-related grade 4 or grade 5 AEs.

\(^{b}\)This row does not represent the total of individual AEs, as each patient may have undergone more than one AE.

\(^{c}\)Grade 3 allergic alveolitis was considered to be a DLT in the patient treated at 50 mg/kg Q2W.
in the safety, full and pharmacokinetics analysis sets (Figure 1). Reasons for discontinuation of enrolled patients prior to treatment included screening failure, withdrawal by physician, worsening performance status (clinical progression) and one death. Patient demographics are presented in Table 1. The median age was 61.5 years (range 40-87), 54% (n = 27) of patients were female. Most patients were Caucasian (90%, n = 45). Primary diagnoses included CRC (50%, n = 25), ovarian carcinoma (20%, n = 10) and NSCLC (14%, n = 7). Patients had been heavily pretreated with chemotherapy, with 84% (n = 42) of patients having received three or more prior regimens. In addition, 34% (n = 17) of patients had received one and 10% (n = 5) of patients had received two prior radiotherapy regimens.

Nineteen patients (38%) in Schedule 1 received imalumab at doses from 1 to 50 mg/kg Q2W and 31 patients in Schedule 2 (62%, including 22 patients in the expansion cohort) received imalumab 10 or 25 mg/kg QW. Overall, the median number of imalumab treatment cycles received was 2 (range 1-17).

Of 68 patients enrolled in the study, all 50 patients who received one or more treatment discontinued treatment because of disease progression according to RECIST v1.1 criteria (76%, n = 38), clinical disease progression (12%, n = 6), an AE (8%, n = 4) or consent withdrawal (4%, n = 2) (Figure 1).

3.2 | Exposure and dose interruptions

Overall, 9 (18%) of the 50 patients who received one or more dose of treatment were exposed to imalumab for <1 month, 33 (66%) from 1 to <4 months, six (12%) from 4 to <7 months and two (4%) patients for ≥10 months.

A total of 41 patients (82%) had no imalumab dose reductions during the study. Of the nine patients (18%) who required one or more dose reduction, six had one reduction and three had more than one dose reduction.

3.3 | Safety

Forty-six (92%) patients who received at least one dose of imalumab had treatment-emergent AEs (TEAEs), the majority of which (84%) were grade 1 or 2 (Supporting Information Tables S1 and S2). Immunologically relevant TEAEs in at least one patient included three (11%) patients with rash and two (7%) with pruritus in the 10 mg/kg QW group. Fifteen (30%) patients had AEs that were considered related to imalumab, with the most common being fatigue (10%) and vomiting (6%) (Table 2). All treatment-related AEs were grade 1 or 2, except for four grade 3 events that occurred in two (4%) patients (all serious adverse events [SAEs]). One of these treatment-related SAEs was grade 3 allergic alveolitis resulting in pulmonary haemorrhage occurring during cycle 1 in a patient receiving 50 mg/kg Q2W. This Caucasian male patient was hospitalized and recovered, receiving therapeutic doses of prednisone for several weeks. The patient had been receiving concomitant therapy including albuterol sulfate, amiodipine besylate, diphenhydramine and fluconazole, and his relevant medical history comprised anxiety-exacerbated asthma, Barrett’s oesophagus, hypertension, seasonal allergies and shortness of breath. The three remaining SAEs (grade 3 vomiting, constipation and nausea, Table 2), in one patient treated with 10 mg/kg QW, were considered to be possibly treatment related; all SAEs resolved without dose modification.

The SAE of grade 3 allergic alveolitis resulting in pulmonary haemorrhage in the first patient treated at the 50 mg/kg Q2W dose level was considered a DLT (ie, a grade 3 nonhaematologic toxicity during the first cycle of treatment). Diagnosis was made clinically via exclusion. Computed tomographic angiography was used to exclude pulmonary embolism and demonstrated the presence of ground-glass opacities in the lungs, suggesting the presence of multifocal broncho-pneumonia. There was no evidence of pulmonary infection. Allergy was suspected as symptoms resolved following treatment with prednisone. Due to the clinical significance of this serious adverse event, treatment at this dose level was suspended. Subsequently, the dose of 37.5 mg/kg every 2 weeks was chosen to be tested and it was found to be the MTD for Schedule 1. In Schedule 2, the MTD was not reached and imalumab was well tolerated up to the highest dose tested (25 mg/kg QW).

Five on-treatment deaths occurred during the study; none were considered related to imalumab. All five deaths were due to disease progression (three in the 10 mg/kg QW cohort, one in the 10 mg/kg Q2W cohort and one in the 37.5 mg/kg cohort).

3.4 | Pharmacokinetics

Area under the curve (AUC) and maximum concentration (Cmax) increased with increasing doses of imalumab (Figure 2). Pharmacokinetic parameters for the most commonly administered dose, 10 mg/kg QW, are shown in Table 3. The t1/2 of imalumab ranged from 56-150 hours (day 1, cycle 1) to 73-176 hours (day 15, cycle 2). The median Cmax increased from 213.0 mg/L (range 122.0-621.0 mg/L) at day 1, cycle 1, to 321.5 mg/L (range 169.0-476.0 mg/L) at day 15, cycle 2. The concentration-time profiles for the Q2W and QW dosing schedules are shown in Figure 3A,B.

3.5 | Immunogenicity

Anti-imalumab antibody data were available for 48 treated patients at baseline and 27 patients at study completion. Seven patients showed detectable anti-imalumab antibodies at one or more visits; they were present at baseline in five patients (one patient each receiving 1 mg/kg and 25 mg/kg Q2W and three patients treated with 10 mg/kg QW) with no subsequent increase after exposure to imalumab. Pre-existing antibodies against imalumab were neutralizing at all time points in one patient, only after exposure to imalumab in three patients and there was no neutralizing activity in the last patient. Two (4%) of 50 patients, both treated with 10 mg/kg QW, developed de novo anti-imalumab binding and neutralizing antibodies at days 58 and 184, respectively.
**FIGURE 2**  Area under the curve and maximum plasma concentration of imalumab given every two weeks (schedule 1) and once weekly (schedule 2). Data plotted are individual patient pharmacokinetic parameter values (estimate) versus actual total body dose of imalumab. AUC$_{\text{INF,obs}}$ area under the plasma concentration-time curve from time zero (pre-dose) extrapolated to infinity (mg*h/L); AUC$_{(0-t)}$ area under the plasma concentration-time curve from time zero (pre-dose) to time ‘t’ (338 hours post-dose for schedule 1 and 168 hours post-dose for schedule 2) (mg*h/L); C$_{\text{max}}$, maximum plasma concentration (mg/L); PK$_{\text{DAY = 1}}$, cycle 1 day 1; PK$_{\text{DAY = 15}}$, cycle 2 day 15. Q2W, every two weeks; QW, every week. The legend shows the treatment schedule, treatment cohort, and imalumab dose level for each data point.

**TABLE 3**  Pharmacokinetic parameters for patients treated with 10 mg/kg weekly

| Time point | Statistic       | AUC(0-inf) (mg*h/L) | AUC(0-tau) (mg*h/L) | C$_{\text{max}}$ (mg/L) | C$_{\text{min}}$ (mg/L) | t$_{1/2}$ (h) | MRT(0-inf) (h) | CL (L/h) | V$_{\text{ss}}$ (L) |
|------------|-----------------|---------------------|---------------------|--------------------------|--------------------------|-------------|--------------|----------|-----------------|
| Cycle 1, day 1 | n | 27 | 27 | 28 | - | 27 | 27 | 27 | 27 |
|            | Mean | 19910 | 14490 | 231.11 | - | 87.00 | 124.8 | 0.04058 | 4.837 |
|            | SD | 6826 | 4437 | 93.82 | - | 20.06 | 29.16 | 0.01259 | 1.045 |
|            | CV% | 34.3 | 30.6 | 40.6 | - | 23.1 | 23.4 | 31.0 | 21.6 |
|            | Minimum | 9930 | 8650 | 122.0 | - | 56.0 | 79.3 | 0.0208 | 3.12 |
|            | Median | 18420 | 13510 | 213.00 | - | 85.60 | 122.5 | 0.02929 | 4.772 |
|            | Maximum | 36400 | 24100 | 621.0 | - | 150 | 214 | 0.0770 | 6.97 |
|            | Geometric mean | 18870 | 13890 | 218.33 | - | 84.97 | 121.8 | 0.03883 | 4.727 |
|            | Geometric CV% | 34.0 | 30.0 | 33.2 | - | 22.4 | 22.8 | 30.9 | 22.4 |
| Cycle 2, day 15 | n | - | 18 | 18 | 18 | 18 | - | 18 | 18 |
|            | Mean | - | 26320 | 313.83 | 83.78 | 118.3 | - | 0.03152 | 5.122 |
|            | SD | - | 9925 | 76.70 | 39.15 | 32.32 | - | 0.01050 | 1.599 |
|            | CV% | - | 37.7 | 24.4 | 46.7 | 27.3 | - | 33.3 | 31.2 |
|            | Minimum | - | 13500 | 169.0 | 33.9 | 72.7 | - | 0.0182 | 2.93 |
|            | Median | - | 26250 | 321.50 | 83.05 | 120.3 | - | 0.02929 | 5.028 |

(Continues)
3.6 | Tumour response

All 50 treated patients were evaluated for response based on RECIST v1.1 criteria; the response was known in 39 patients and unknown in 11. The best overall response was stable disease (SD) in 13 patients (26.0% of total treated patients, 33.3% of those with known response), and progressive disease in 26 patients (52% of total treated patients, 66.7% of those with known response). Three patients with SD were treated at 3 mg/kg Q2W, three at 10 mg/kg Q2W, four at 10 mg/kg QW, and one each at 1 mg/kg Q2W, 25 mg/kg Q2W and 25 mg/kg QW. Of the 13 patients with SD, eight had SD lasting for more than 4 months. There were no complete or partial objective tumour responses or evidence of a dose response (Supporting Information Figure S2 and Supporting Information Table S3). The tumour types of patients with SD of greater than 4 months included NSCLC (n = 2), ovarian cancer (n = 2), CRC (n = 1); oesophageal cancer (n = 1), and cancer of the parotid gland (n = 1). Median time on treatment for those with SD of greater than 4 months was 5.44 months (range 4.37-15.64). One patient with ovarian cancer (granulosa cell tumour) received 10 mg/kg QW imalumab for 17 cycles.

3.7 | Pharmacodynamics

3.7.1 | Levels of circulating oxMIF and total MIF

Across all patients in the study, the median level of circulating oxMIF remained at 4.75 ng/mL, although the range varied from
4.75-15.98 at baseline (n = 50) to 4.75-9.59 at cycle 4 (n = 10) and 4.75-4.75 at study completion (n = 2) (Table 4). The median level of total plasma MIF (oxMIF plus redMIF) in all patients also remained at 4.75 ng/mL, with a range of 4.75-27.78 (n = 50) at baseline, 4.75-10.57 (n = 10) at cycle 4 and 4.75-4.75 (n = 2) at study completion (Table 4). There were no notable changes from baseline in plasma levels of circulating oxMIF and total MIF.

### TABLE 4
Concentrations of circulating oxMIF and total plasma MIF in the safety population

|          | Patients (n) | Median circulating oxMIF (range), ng/mL | Median total MIF (range), ng/mL |
|----------|--------------|----------------------------------------|----------------------------------|
| Baseline | 50           | 4.75 (4.75–15.98)                      | 4.75 (4.75–27.78)                |
| Cycle 2  | 41           | 4.75 (4.75–13.01)                      | 4.75 (4.75–11.94)                |
| Cycle 3  | 13           | 4.75 (4.75–9.33)                       | 4.75 (4.75–11.00)                |
| Cycle 4  | 10           | 4.75 (4.75–9.59)                       | 4.75 (4.75–10.57)                |
| Cycle 5  | 6            | 4.75 (4.75–6.80)                       | 4.75 (4.75–10.02)                |
| Cycle 6  | 7            | 4.75 (4.75–22.73)                      | 4.75 (4.75–24.74)                |
| Cycle 7  | 3            | 4.75 (4.75–4.75)                       | 4.75 (4.75–4.75)                 |
| Cycle 8  | 1            | 4.75 (4.75–4.75)                       | 4.75 (4.75–4.75)                 |
| Cycle 9  | 2            | 4.75 (4.75–4.75)                       | 4.75 (4.75–4.75)                 |
| Cycle 10 | 2            | 4.75 (4.75–4.75)                       | 4.75 (4.75–4.75)                 |
| Cycle 11 | 2            | 4.75 (4.75–4.75)                       | 4.75 (4.75–4.75)                 |
| Cycle 12 | 2            | 4.75 (4.75–4.75)                       | 4.75 (4.75–4.75)                 |
| Cycle 13 | 2            | 4.75 (4.75–4.75)                       | 4.75 (4.75–4.75)                 |
| Cycle 14 | 1            | 4.75 (4.75–4.75)                       | 4.75 (4.75–4.75)                 |
| Cycle 15 | 1            | 4.75 (4.75–4.75)                       | 4.75 (4.75–4.75)                 |
| Cycle 16 | 1            | 4.75 (4.75–4.75)                       | 4.75 (4.75–4.75)                 |
| Cycle 17 | 1            | 4.75 (4.75–4.75)                       | 4.75 (4.75–4.75)                 |
| Completion | 2           | 4.75 (4.75–4.75)                       | 4.75 (4.75–4.75)                 |

Baseline measurement is pre-cycle 1 dose. All other measurements are pre-dose. MIF, macrophage migration inhibitory factor; oxMIF, oxidized macrophage migration inhibitory factor.

### Discussion

Imalumab is an inhibitor of oxMIF, whose significance as a tumour-related conformational isoform of MIF has only been reported relatively recently. Although cancer immunotherapy was initiated in the 1980s, it only reached widespread recognition as a breakthrough treatment in 2013; we initiated our first-in-human anti-oxMIF antibody study in 2012.

The limited assessment in this phase 1 study did not reveal any safety concern with imalumab in patients with advanced solid tumours at doses up to 37.5 mg/kg Q2W. The DLT was allergic alveolitis, an interstitial inflammation of the distal lung involving alveolar macrophage activation and antibody-dependent inflammation. No data regarding antibody titre were collected for this patient. Immunologically related AEs are usually not considered to be dose-related or DLTs due to their idiosyncratic nature and the DLT of allergic alveolitis was observed in a patient with a history of shortness of breath, asthma and allergic conditions. However, it has been shown to be related to biologic therapies in previous studies. As MIF promotes the release of cytokines, including tumour necrosis factor α, there is the possibility of similar complications with imalumab, such as interstitial lung disease/noninfectious pulmonary complications.

![Figure 4](image-url)  
**Figure 4**  
Tissue penetration (a) and target occupancy (B) showing imalumab binding to oxMIF in mCRC tumour tissue. (A) Example tissue penetration illustrated by stained regions: Consecutive slides were stained for imalumab and oxMIF. Target occupancy was calculated based on digital image analysis. (B) Target occupancy in a patient with mCRC: Median target occupancy in total tumour tissue (tumor + stroma) reached 102% after the first treatment cycle and increased to 119% after the second cycle. Patient was treated with 10 mg/kg imalumab, QW. C2D1, cycle 2, day 1; C2D28, cycle 2, day 28; mCRC, metastatic colorectal cancer; oxMIF, oxidized macrophage migration inhibitory factor; QW, weekly
The assessed pharmacokinetic parameters suggest a potentially subproportional increase of systematic exposure with increasing total dose. However, due to the large range of doses tested and small sample sizes in Schedule 1 dose cohorts and the 25 mg/kg QW dose cohort in Schedule 2, the results should be interpreted with caution.

Despite a heavily pretreated patient population, disease stabilized in approximately a quarter of patients, with durable SD after treatment with imalumab for more than 4 months in eight patients (16% of treated patients), and over 15 months for one patient with ovarian cancer. When evaluating tumour types that had prolonged stable disease, patients with immune-responsive tumours such as NSCLC, ovarian and oesophageal appear to benefit, although the molecular profiles of these tumours are unavailable. This study chose to focus expansion in patients with mCRC based on preclinical data,9,15,16 although limited clinical activity was seen with imalumab in these tumours. In addition, the microsatellite status of the patients with mCRC is unknown, which would be relevant considering the activity of immunotherapy in high-level microsatellite instability mCRC tumors.24,27

MIF appears to promote tumour growth in nonclinical studies of breast cancer,28 glioblastoma29 and childhood rhabdomyosarcoma30 models, and pancreatic cancer,31,32 CRC and osteosarcoma33,34 cell lines. Conversely, MIF downregulation appears to drive antiangiogenic therapy resistance in glioblastoma xenograft models,35 and MIF appears to have tumour-suppressive activity in murine skin.26

The varying biological consequences of MIF oxidation at different sites point to more than one form of ‘oxMIF’. The impact of MIF and its associated pathways are therefore complex and the effect of anti-oxMIF treatment may require additional exploration with chemotheraphy, as anti-oxMIF antibodies have been found to sensitize human prostate and ovarian cancer cell lines to cytotoxic drugs.16

Levels of circulating oxMIF and total MIF (oxMIF plus redMIF) remained steady during treatment with imalumab, and the corresponding median values of oxMIF and total MIF suggested that there was a lack of redMIF present. We are unclear on any direct effect from the blockade of oxMIF with imalumab and its impact on pathway regulation. A previous report of median oxMIF levels in patients with various cancers ranged from 0.0 to 3.5 ng/mL, although a considerable interpatient variation was observed, similar to findings in this study, and we observed higher median levels of 4.75 ng/mL in evaluable patients.15,16 Also aligned with our results, plasma levels of oxMIF in this study, and we observed higher median levels of 4.75 ng/mL in evaluable patients.16

A biologically active dose of imalumab was determined as 10 mg/kg QW based on its safety, pharmacokinetic and pharmacodynamic profile, penetration of tumour tissue and high oxMIF target occupancy. There was an insufficient number of samples from higher doses to confirm a dose-response relationship.

A phase I/IIa imalumab monotherapy study in patients with malignant ascites of ovarian cancer was initiated in 2015 but was terminated prematurely for logistic reasons due to poor design and patient enrolment. A phase Ila combination study investigating imalumab plus 5-fluorouracil/leucovorin or panitumumab versus standard of care in patients with mCRC was initiated in 2015 but was terminated prematurely based on an overall benefit-risk assessment by the data safety monitoring board after a review of the available safety and efficacy data. Although no clinical studies evaluating imalumab in advanced solid tumours are currently planned, future clinical development would require integrative biomarkers in order to predict response.

In conclusion, imalumab had a maximum tolerated dose of 37.5 mg/kg Q2W in patients with advanced solid tumours, with a biologically active dose of 10 mg/kg QW. Further clinical investigation is warranted to assess the role of oxMIF as a therapeutic target in humans based on preclinical evidence suggesting that it may play a role in carcinogenesis and cancer-associated inflammation. The modest antitumor activity observed in the present study may be enhanced by combining oxMIF-targeted treatments with other anticancer agents, with the caveat that there may be additional toxicity with addition of these agents.37

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CONTRIBUTORS
A.M.T., D.M., D.V., J.C.S. and R.R. designed the research. A.M.T., A.Y., D.M., J.C.S., J.S., M.P. and N.H. performed the research. A.M.T., A.Y., D.M., D.V., F.d.J., J.C.S., M.P. and N.H. analysed the data. A.M.T., A.Y., D.M., D.V., F.d.J., J.C.S., J.S., L.H., M.P., N.H. and R.R. wrote the manuscript. A.M.T. and L.H. provided patient care, evaluations and accrual. A.Y. provided support with literature and references. A.M.T., D.M. and J.S. provided administrative, technical and material support. A.M.T., D.M., M.P. and J.C.S. provided study supervision.

DATA AVAILABILITY STATEMENT
The datasets, including the redacted study protocol, redacted statistical analysis plan, and individual participant data supporting the results, will be available 3 months after the submission to researchers who provide a methodologically sound proposal. The data will be provided after de-identification, in compliance with applicable privacy laws, data protection and requirements for consent and anonymization.

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