BMJ Oncology

First-in-human phase 1 dose-escalation study of W0180, an anti-VISTA monoclonal antibody, with and without pembrolizumab in patients with locally advanced or metastatic solid tumours

Carlos Gomez-Roca,[1] Stéphane Champiat,[2,3] Francois-Xavier Danlos,[2] Eduardo Castañón Álvarez,[4] Philippe Alexandre Cassier ,[5] Elena Dupuy,[6] David Jegou,[6] Marie Primard,[6] Aurélie Pétain,[6] Mathilde Saccareau,[6] Geneviève Gueguen-Dorbes,[6] Claire Fabre,[6] Aurélien Marabelle ,[2] Ignacio Melero [7,8]

To cite: Gomez-Roca C, Champiat S, Danlos F-X, *et al*. First-in-human phase 1 dose-escalation study of W0180, an anti-VISTA monoclonal antibody, with and without pembrolizumab in patients with locally advanced or metastatic solid tumours. *BMJ Oncology* 2026;**5**:e000854. doi:10.1136/bmjonc-2025-000854

CG-R and AM contributed equally.

Received 19 May 2025
Accepted 20 January 2026

For numbered affiliations see end of article.

Correspondence to
Professor Aurélien Marabelle; aurelien.marabelle@gustaveroussy.fr

ABSTRACT

Objective W0180 is a humanised IgG1κ antagonistic monoclonal antibody against the V domain-containing immunoglobulin suppressor of T-cell activation (VISTA) designed to enhance antitumour activities by inhibiting the immunosuppressive role of VISTA in myeloid cells and T cells in solid tumours.

Methods and analysis Preclinical experiments evaluated the pharmacodynamics and antitumour activity of W0180. A first-in-human phase 1 dose-escalation study investigated the maximum tolerated dose (MTD), safety/tolerability, preliminary efficacy, pharmacokinetics and pharmacodynamics of W0180, both as monotherapy and in combination with pembrolizumab (an anti-programmed cell death protein-1 (PD-1) therapy), with the aim of establishing a recommended dose for expansion (RDE). In the monotherapy arm, cohorts of patients with locally advanced/metastatic solid tumours received once-weekly W0180 at increasing doses (from 3.5 to 600 mg). In the combination therapy arm, patients with relapsed/refractory, advanced/metastatic solid tumours and ≥1 prior anti-PD (ligand)-1 therapy line received W0180 (60 or 300 mg)+pembrolizumab.

Results W0180 exhibited pH-independent blockade of the VISTA-ligand interaction in vitro and showed antitumour activity in a syngeneic preclinical murine model expressing human VISTA. In the phase 1 study, of the 33 patients in the monotherapy (n=24) or combination therapy (n=9) arms, 28 contributed to dose determination. Dose-limiting toxicities were Grade 2 cerebral infarction and Grade 3 infusion-related reaction (IRR; n=1 each). The study was terminated prematurely in the dose-escalation phase (due to a business decision by the sponsor) before the MTD/RDE was reached. Common related treatment-emergent adverse events were IRR and fatigue; most were of mild severity. No patients achieved Response Evaluation Criteria in Solid Tumours objective response; two had prolonged stable disease (SD; one from each arm). Biomarker analysis suggested a dose-dependent pharmacodynamic effect of W0180.

Conclusion W0180 demonstrated manageable safety, preliminary signs of clinical activity with prolonged SD and dose-dependent pharmacodynamics consistent with preclinical data (even though MTD was not reached) in patients with locally advanced/metastatic tumours, both as monotherapy and in combination with anti-programmed cell death protein-1 therapy.

Trial registration number NCT04564417.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ V domain-containing immunoglobulin suppressor of T-cell activation (VISTA) has an immunosuppressive role in the tumour microenvironment. W0180 is a humanised IgG1κ antagonistic monoclonal antibody designed to inhibit VISTA and enhance the antitumour activities of myeloid cells and T cells in solid tumours.

WHAT THIS STUDY ADDS

⇒ The results of this first-in-human trial showed that W0180, administered as monotherapy or in combination with anti-PD-1 therapy, has a manageable safety profile and demonstrated preliminary signs of clinical activity with prolonged stable disease and dose-dependent pharmacodynamics consistent with preclinical data in patients with locally advanced/metastatic tumours.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Despite the encouraging results from this study, the regulatory role of VISTA in anti-cancer immunity remains to be fully elucidated. Further prospective studies are needed to investigate therapeutic approaches targeting the VISTA pathway.

INTRODUCTION

The V domain-containing immunoglobulin (Ig) suppressor of T-cell activation (VISTA)

is a type I Ig membrane protein with an extracellular domain that is homologous to programmed cell death ligand-1 (PD-L1).[1] VISTA is a negative checkpoint regulator of immune response and is normally expressed at high levels on myeloid-derived cells (eg, neutrophils, monocytes, macrophages and dendritic cells) and at low levels on naïve CD4+, CD8+ and regulatory T cells.[2] VISTA expression also occurs within the tumour microenvironment (TME), particularly on CD68+ macrophages and myeloid-derived-suppressor cells, which leads to down-modulation of T-cell activation.[3–5]

VISTA acts both as a ligand and a receptor and has two confirmed binding partners on T cells, P-selectin glycoprotein ligand-1 (PSGL1) and V-set and immunoglobulin domain containing (VSIG)-3, as well as two unconfirmed ligands, VSIG-8 and galectin-9.[6 7] The VISTA-PSGL1 interaction occurs at acidic pH, whereas VISTA-VSIG-3 binding occurs at physiological pH.[6] Loss of VISTA expression in vivo (by gene deletion in a murine model) resulted in enhanced T-cell activation and increased production of cytokines, including interferon (IFN)-γ, interleukin (IL)-17A and tumour necrosis factor (TNF)-α.[8 9] Furthermore, the combination of anti-VISTA and anti-PD-L1 antibodies in another murine model was associated with enhanced antitumour activity compared with either antibody alone.[10]

In vitro experiments have shown an enhanced T-cell response after addition of anti-VISTA antibodies to VISTA-positive myeloid antigen presenting cells, consistent with VISTA-mediated immunosuppression.[1] In addition, antibody-mediated inhibition of VISTA binding has shown potential in multiple tumour models, providing synergistic blockade with other inhibitory immune checkpoints.[11] As such, immunosuppression by VISTA-expressing TME is thought to be an underlying mechanism of resistance to cancer immunotherapy.[12 13] In addition, upregulation of VISTA expression on CD68+ macrophages may act as a compensatory inhibitory pathway, as reported after anti-cytotoxic T-lymphocyte associated protein 4 (CTLA4) treatment (ipilimumab) in prostate cancer.[12] Therefore, VISTA inhibition in the TME may be a potential therapeutic strategy for enhancing antitumour response.[14]

W0180 (also known as K01401-020) is a first-in-class, humanised IgG1κ monoclonal antibody against VISTA that is expected to restore T-cell immune response. W0180 binds with high affinity to the extracellular domain of cynomolgus monkey-VISTA and human-VISTA (hVISTA), with an equilibrium dissociation constant of ~0.1 nM.[15] In vitro, W0180 stimulated IFN-γ release from human peripheral blood mononuclear cells (PBMCs) in a mixed lymphocyte reaction setting, increased natural killer (NK) cell proliferation and induced cytokine production by NK cells and monocytes, thereby contributing to T-cell activation.[15] In vivo, W0180 as monotherapy or in combination with the anti-programmed cell death protein-1 (PD-1) antibody pembrolizumab for 4 weeks was well tolerated in a non-human primate model, while peripheral blood sampling showed dendritic cell activation and complete VISTA occupancy by W0180. Treatment with W0180 also led to increased PD-L1 expression on myeloid cells, suggesting that combination with an anti-PD(L)-1 agent may enhance antitumour activity.[15]

In this article, we report the preclinical characterisation of W0180 and the findings of the first-in-human phase 1 study of this anti-VISTA monoclonal antibody in patients with locally advanced or metastatic solid tumours.

METHODS

Preclinical experiments

Preclinical characterisation of the anti-VISTA antibody W0180 included in vitro binding assays, monocyte activation assays and evaluation of in vivo antitumour activity in a syngeneic tumour model established in hVISTA knock-in mice. The methods for these experiments are described in detail in the online supplemental methods.

First-in-human clinical study design

An open-label, multicentre, phase 1 dose-escalation study was conducted at three centres in France and two centres in Spain in adult patients with locally advanced or metastatic solid tumours (ClinicalTrials.gov identifier: NCT04564417).

Increasing W0180 dose levels were administered, either as monotherapy or in combination with pembrolizumab, until the maximum tolerated dose (MTD) or the recommended dose for expansion (RDE) was established (online supplemental figure S1). The 3.5 mg first-in-human dose was determined according to both the no observed adverse effect levels and minimal anticipated biological effect level approaches. Predictions of pharmacokinetics and peripheral target occupancy at 3.5 mg gave an acceptable maximal target occupancy of 20% and a maximal concentration in the range of the first active concentrations in in vitro tests. An accelerated titration design was used for the first three W0180 monotherapy doses (3.5 mg, 15 mg, 60 mg). This was followed by a standard 3+3 dose-escalation up to a maximum dose of 600 mg, based on the recommendations of the Safety Monitoring Board (SMB). The SMB met prior to each dose escalation and was tasked with assessing safety, pharmacokinetic and, when available, immunogenicity and pharmacodynamic data, and with making recommendations on continuing or terminating administration or recruitment at each dose and on modifying the next dose level. Co-administration of W0180+pembrolizumab was conducted on the recommendations of the SMB, using standard 3+3 dose-escalation for W0180 from 60 mg up to a maximum of 300 mg. The starting dose for the W0180 combination therapy was at least one dose level below the last W0180 monotherapy dose level that had been demonstrated to be safe according to SMB recommendation. To confirm the MTD and/or RDE, six patients were needed in each dose level cohort at the MTD and/or RDE.

The study was conducted in accordance with the study protocol approved by institutional review boards/

independent ethics committees; the study protocol is available in the online supplemental file 2. The study was also guided by the ethical principles derived from the Declaration of Helsinki, applicable International Council of Harmonisation Good Clinical Practice guidelines, and all applicable laws and regulations. Patients provided written informed consent before participating in the phase 1 study. According to the SMB charter, the SMB was composed of skilled people with broad expertise in phase 1 clinical trials in oncology, according to their curriculum vitae and previous experiences in clinical studies.

Patient involvement

Patients were not involved in the design, management or conduct of the trial.

Patients

The W0180 monotherapy arm included patients with histologically or cytologically confirmed locally advanced or metastatic solid tumours that had progressed or were refractory to standard treatment. Other key inclusion criteria were: age ≥18 years; Eastern Cooperative Oncology Group performance status (ECOG PS) ≤1; evidence of measurable disease as determined by Response Evaluation Criteria in Solid Tumours (RECIST) V.1.1[16]; and adequate organ function, blood counts and biochemistry test results. Key exclusion criteria were: previous anti-VISTA treatment; central nervous system metastases and/or carcinomatous meningitis; a history of Grade ≥3 immune-related adverse events (irAEs) leading to discontinuation of prior anti-PD(L)-1 or stimulatory/co-inhibitor T-cell receptor targeted therapy; inadequate cardiac function or uncontrolled hypertension; active autoimmune disease (known or suspected) and a current or past history of interstitial lung disease.

The W0180+pembrolizumab combination therapy arm enrolled patients with advanced or metastatic solid tumours who were relapsing after or refractory to ≥1 prior line of anti-PD(L)-1 therapy in the metastatic setting.

Treatment

W0180 and pembrolizumab were both administered by intravenous infusion. When co-administered with pembrolizumab, W0180 was infused 15–30 min after the end of the pembrolizumab infusion.

For W0180 monotherapy, each 21-day treatment cycle consisted of W0180 administration on Days 1, 8 and 15. For W0180+pembrolizumab combination therapy, each 21-day treatment cycle consisted of pembrolizumab administration on Day 1 and W0180 administration on Days 1, 8 and 15.

The original study protocol did not specify prophylaxis to reduce the risk of infusion-related reactions (IRR) or cytokine release syndrome (CRS). However, during the study, the protocol was amended to introduce a defined systemic prophylaxis for IRR or CRS; this was to be administered before each infusion and included corticosteroids, an antipyretic and an antihistamine (H1 receptor antagonist).

Study treatment was continued until confirmed disease progression, unacceptable toxicity, patient request to discontinue treatment, administration of other anti-cancer therapy, withdrawal of consent or death, whichever occurred first or at the investigator's discretion.

Outcomes

The primary objective was to determine the MTD and describe dose-limiting toxicities (DLTs) with W0180 administered as monotherapy and in combination with pembrolizumab.

The MTD was defined as the highest dose where >33% of patients developed a DLT during the 21-day DLT observation period (ie, between the initial study drug infusion in the first 21-day treatment cycle (Cycle 1) and the initial study drug infusion in Cycle 2). DLTs were defined as adverse events (AEs) or abnormal laboratory values that were assessed as being: (a) at least possibly related to the study drug; (b) clinically relevant and (c) unrelated to disease, disease progression, concurrent illness or concomitant medications. The criteria for defining DLTs are provided in online supplemental table S1.

The secondary objectives included determination of the RDE, evaluation of the safety/tolerability, preliminary antitumour activity, pharmacokinetics and immunogenicity of W0180 as monotherapy and in combination with pembrolizumab. Determination of the RDE was based on SMB recommendation and review of all available information, including treatment-emergent AEs (TEAEs), pharmacokinetic parameters and, when available, immunogenicity and pharmacodynamics data.

Exploratory endpoints included the evaluation of W0180 pharmacodynamic activity in blood and TME from patients biopsies.

Safety assessments

For each dose level of the W0180 monotherapy and W0180+pembrolizumab combination therapy arms, a safety interval of ≥7 days was applied between the first and subsequent patients. DLTs were determined during Cycle 1 and graded according to the Common Terminology Criteria for Adverse Events (CTCAE), V.5.0.

The 3+3 model was used for dose escalation of W0180 (as monotherapy and in combination with pembrolizumab), in which three or six patients were treated at each dose level depending on the incidence of DLTs (online supplemental figure S1). These safety rules were also applied if a Grade 2 treatment-related AE occurred during Cycle 1 in the accelerated titration dose levels. Patients who experience DLTs at any dose level received appropriate treatment and supportive care as necessary and were carefully monitored until resolution or stabilisation of the AE to Grade 1 or baseline.

Efficacy assessments

Tumour response was assessed locally as per RECIST, V.1.1[16] and immune RECIST (iRECIST; for tumour response to immunotherapy).[17] Appropriately calibrated imaging (CT (preferable) or MRI) was performed at baseline and during follow-up to characterise each identified lesion. Tumour assessment was performed every 6 weeks from the first dose for the first 12 months, then every 9 weeks until confirmed RECIST/iRECIST disease progression, withdrawal of consent, administration of other anticancer therapy, loss to follow-up or death (whichever occurred first).

Pharmacokinetic analysis

The pharmacokinetic profile of W0180 was evaluated using serum samples collected during Cycle 1, Day 1 and Cycle 1, Day 15 at pre-dose, end of infusion and 4, 8, 24, 48, 72 and 96 hours post-infusion. Pharmacokinetic parameters were assessed using validated non-compartmental methods (WinNonlin).[18]

Immunogenicity analysis

The presence of anti-drug antibodies (ADA) was assessed at baseline and pre-administration of Cycles 2 and 4, and then pre-administration every two cycles for up to 6 months. The detection and characterisation of anti-W0180 antibodies was performed using a validated assay method by/under the supervision of the sponsor.

Pharmacodynamic analysis

The ability of W0180, as monotherapy and in combination with pembrolizumab, to induce immune cell activation was evaluated by assessing the modulation of several biomarkers. A panel of serum pro-inflammatory cytokines and chemokines was assessed as potential surrogates for immune cell activation at baseline, Day 1 (at the end of the infusion and at 4 hours post-infusion) and Day 8 (pre-dose). Meso Scale Discovery (MSD) multiplex assays were used to detect IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, macrophage inflammatory protein 1 (MIP1)-α, MIP1-β, monocyte chemoattractant protein-1 (MCP-1), MCP-4 and macrophage-derived chemokine, with levels measured using the MSD Sector Imager 6000 reader. C-X-C motif chemokine ligand (CXCL) 9 levels were measured by ELISA method using the CXCL9/MIG Quantikine ELISA Kit (R&D Systems, Minneapolis, Minnesota, USA) and Ensight plate reader (PerkinElmer, Waltham, Massachusetts, USA) following the manufacturer's protocol. Standard methods of immunophenotyping were used to detect CD8+ and CD4+ T cells, NK cells and monocytes by flow cytometry. Fresh peripheral whole blood samples collected in NaHep were evaluated by flow cytometry (BD Biosciences Fortessa X-20). Monoclonal antibodies used for flow cytometry panel included: anti-CD3, anti-CD45, anti-CD56, anti Ki-67 and anti-CD137 from BioLegend; anti-CD4, anti-CD8, granzyme B, anti-CD14 and anti-CD16 from BD. Samples after antibody incubation were acquired on the Fortessa instrument and a maximum of 250 000 events. Gating on targeted populations (T cells, monocytes, NK cells) was analysed using FlowJo Software.

To assess changes in the number of tumour-infiltrating lymphocytes (TILs), tumour tissue samples were collected at baseline (fresh or archival tissue if available) and on Day 8 of Cycle 2 (fresh tissue). TILs were identified by immunofluorescence and image analysis for quantification.

Retrospective analysis for determining the VISTA and PD-L1 expression level at baseline was conducted by a pathologist using immunohistochemistry of archival or fresh tissue biopsies that were collected before the first infusion. The VISTA H-score was calculated from the percentage of tumour cells with no (0), low (1+), moderate (2+) or strong (3+) staining. The VISTA H-score was reported as a whole number between 1 and 300, unless VISTA expression was not negative but <1% (in which case, the VISTA H-score was 0.5). PD-L1 staining was quantified using the combined positive score (CPS) methodology.

Statistical analysis

While the sample size during a dose-escalation study cannot be precisely determined as it depends on the observed toxicity, it was planned to include approximately 39 evaluable patients (21 in the single agent part and 18 in the combination dose part).

In the clinical study, descriptive methods were used to summarise results. Continuous data were summarised by median, range and 95% CIs, where relevant. Categorical data were presented as frequency and percentage.

Pharmacokinetic, immunogenicity and pharmacodynamic analyses were conducted using data from the full analysis set (FAS; defined as all enrolled patients who received at least one dose of study drug). Safety and efficacy assessments were conducted using data from the dose-determining set (DDS; defined as patients who met the minimum exposure criteria (received at least 90% of the scheduled dose of W0180±pembrolizumab during cycle 1) and had scheduled safety evaluations or those who discontinued earlier due to a DLT).

Comparison of the modulations in immune cell populations (expressed as log fold-change (log FC)) between before and after W0180 administration was tested using the Wilcoxon signed rank test, with the null hypothesis that the distribution of the maximum log FC was symmetric about 0. The significance level was set at $p<0.05$.

RESULTS

Preclinical study

W0180 is a pH-independent antagonistic anti-VISTA cancer immunotherapy

In vitro binding assays showed that the anti-VISTA antibody W0180 blocked the interaction between VISTA and its ligands at pH 6 and pH 7.4 (online supplemental figure S2). W0180 also induced expression of monocyte

activation markers and CXCL10 (or IFN-γ-induced protein 10 (IP10)) release in monocyte activation assays (online supplemental figure S3).

In vivo, the murinised form of W0180 (AB462) induced tumour growth inhibition when administered as monotherapy in a MC-38 murine model established in hVISTA-knock-in (hVISTA-KI) mice and induced synergistic antitumour activity when co-administered with murinised anti-PD-1 antibody (RMP1-14; online supplemental figure S4).

W0180 first-in-human study

Participants

In total, 33 patients with locally advanced or metastatic solid tumours were included in the FAS between September 2020 and April 2023. As per the study protocol, 24 patients received W0180 monotherapy and nine patients received W0180+pembrolizumab combination therapy (table 1). Five patients from the monotherapy group were not evaluable for DLT, so were excluded from the DDS.

The demographics of patients included in the FAS are summarised in table 1. Across all 33 patients, 17 patients (51.5%) had a baseline ECOG PS score of 0 and 16 patients (48.5%) had a baseline ECOG PS score of 1. The primary tumour site was diverse in both treatment arms; the most common tumour sites (in ≥2 patients) were the pancreas (n=5; 20.8%), skin (n=3; 12.5%) and breast (n=2; 8.3%) in the monotherapy arm, and skin (n=2; 22.2%) in the combination therapy arm. Prior immunotherapies were received by 8 (33.3%) and 9 (100.0%) patients in the monotherapy and combination arm, respectively. The most common prior immunotherapy received was pembrolizumab and nivolumab.

Table 1 Patient demographics and baseline characteristics in the full analysis set (n=33)

	Monotherapy (n=24)	Combination therapy (n=9)
Age, years	56 (38–83)	61 (43–72)
≥65 years, n (%)	7 (29.2)	4 (44.4)
Male, n (%)	17 (70.8)	7 (77.8)
ECOG PS, n (%)		
0	11 (45.8)	6 (66.7)
1	13 (54.2)	3 (33.3)
Time since diagnosis, months	38.47 (5.10–285.27)	71.20 (21.32–138.84)
Time since last relapse/progression, months	1.55 (0.72–5.98)	1.38 (0.92–4.96)
Number of prior treatment regimens, n (%)		
0	1 (4.2)	0
1	3 (12.5)	0
2	5 (20.8)	0
≥3	15 (62.5)	9 (100.0)
Prior immunotherapy, n (%)	8 (33.3)*	9 (100.0)
Pembrolizumab	5 (20.8)	4 (44.4)
Nivolumab	5 (20.8)	6 (66.7)
Atezolizumab	1 (4.2)	1 (11.1)
Cemiplimab	1 (4.2)	0
Durvalumab	0	2 (22.2)
Primary site of tumour, n (%)		
Pancreas	5 (20.8)	0
Skin	3 (12.5)	2 (22.2)
Breast	2 (8.3)	0
Other	14 (58.3)†	7 (77.8)‡

Data are presented as median (range) unless stated otherwise.
*The proportion of patients who received prior immunotherapy in the monotherapy group was low as most patients either had a cancer indication for which anti-PD-1/PD-L1 treatment was not FDA-approved at the time of the study (see figure 1), or a PD-L1 expression level (CPS) <10, thus was unlikely to be eligible to immunotherapy.
†Other primary tumour sites were head and neck, intestine, mesothelium, pectoral, uveal melanoma, ampulla of Vater, suprarenal, kidney, ovary, appendix, liver, salivary gland, uterus and trachea (n=1 each).
‡Other primary tumour sites were head and neck, mesothelium, left forehead bone, liver, bladder, kidney and unknown (n=1 each).
CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-1, programmed cell death protein-1; PD-L1, programmed death ligand-1.

W0180 drug exposure

Patients received W0180 doses of 3.5–600 mg once weekly (QW) in the monotherapy arm and 60 or 300 mg QW in the combination therapy arm. In the DDS, the median (range) duration of W0180 exposure was 6.1 (2.4–74.4) weeks with monotherapy and 12.0 (4.9–62.0) weeks with combination therapy.

Safety/tolerability profile of W0180

Of the 28 patients in the DDS who received W0180, DLTs were reported in two patients.

One patient in the monotherapy arm (W0180 600 mg dose-level cohort) developed a Grade 2 cerebral infarction in the right middle cerebral artery on Day 17 of Cycle 1, which was determined to be of probable atherothrombotic origin. This 41-year-old patient had Stage IV adenoid cystic carcinoma of salivary gland with hepatic, pleural and pulmonary metastases and had previously undergone radiation therapy within the submandibular area and resection of the right submaxillary gland and lymph nodes. The AE was considered possibly related to the treatment because the patient had no relevant medical history, especially cardiovascular, and was a non-smoker. After the development of the Grade 2 cerebral infarction, W0180 treatment was discontinued; the patient received aspirin, atorvastatin and clopidogrel and subsequently recovered with sequelae.

The second patient, who was in the combination therapy arm (W0180 300 mg dose-level cohort), experienced a Grade 3 IRR on Day 1 of Cycle 1. This 66-year-old

Table 2 Related treatment-emergent adverse events in the dose-determining set (n=28)

Related TEAE PT, n (%)	All grades	Grade ≥3
Any related TEAE	28 (100.0)	9 (32.1)
IRR	27 (96.4)	4 (14.3)
Fatigue	8 (28.6)	0
Neutropenia	6 (21.4)	6 (21.4)
Fever	6 (21.4)	0
ALT increased	5 (17.9)	1 (3.6)
Nausea	4 (14.3)	0
Thrombocytopenia	4 (14.3)	0
Vomiting	4 (14.3)	0
Headache	3 (10.7)	0
AST increased	2 (7.1)	1 (3.6)
Asthenia	2 (7.1)	0
Chills	2 (7.1)	0
Decreased appetite	2 (7.1)	0
Diarrhoea	2 (7.1)	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase; IRR, infusion related reaction; PT, preferred term; TEAE, treatment-emergent adverse event.

patient had Stage IV malignant melanoma and a medical history of adrenal insufficiency. The patient had received IRR prophylaxis with ketoprofen and dexchlorpheniramine prior to W0180 administration. After the onset of the Grade 3 IRR, W0180 treatment was interrupted, and the patient was successfully treated with symptomatic treatment routinely used by the site in accordance with standard practice. The patient subsequently resumed combination therapy at a reduced W0180 dose of 60 mg, but later discontinued treatment at Cycle 11 due to a TEAE (second malignant cancer).

The most common TEAEs (in ≥15% of patients) in the monotherapy and combination therapy arms are shown in online supplemental tables S2 and S3, respectively.

All patients experienced at least one related TEAE in the monotherapy and combination therapy arms (table 2 and online supplemental table S4). In the monotherapy arm (n=19), the most common related TEAEs were IRR, fatigue, neutropenia, fever, alanine aminotransferase (ALT) increased, thrombocytopenia and vomiting. In the combination therapy arm (n=9), the most common TEAEs were IRR, fatigue and diarrhoea. The safety profile of W0180 was not affected by the addition of pembrolizumab with regard to the nature, severity or frequency of related TEAEs.

Most related TEAEs were of mild severity (ie, Grade 1–2). Grade ≥3 related TEAEs were neutropenia in six patients (21.4%; five in the monotherapy arm and one in the combination therapy arm), IRR in four patients (14.3%; three in the monotherapy arm and one in the combination therapy arm), aspartate aminotransferase increased in one patient (3.6%; in the monotherapy arm) and ALT increased in one patient (3.6%; in the monotherapy arm).

TEAEs led to discontinuation of W01080 in two patients in the monotherapy arm (one in the W0180 15 mg dose-level cohort (with acute pericarditis) and one in the W0180 600 mg dose-level cohort (with treatment-related Grade 2 cerebral infarction)) and of W01080+pembrolizumab in three patients in the combination therapy arm (one with W0180 60 mg+pembrolizumab (myocarditis) and two with W0180 300 mg+pembrolizumab (one with polyarthritis and one with a second malignant cancer); figure 1).

Two TEAEs led to death; neither of these was considered related to W0180 treatment.

The phase 1 study was terminated prematurely in the dose escalation part of the study before the MTD/RDE could be reached due to a business decision.

Preliminary antitumour activity of W0180 as monotherapy and combination with pembrolizumab

The tumour response to W0180 in each patient is presented in online supplemental figure S5.

In the monotherapy arm (n=19), no patients achieved objective response (ie, complete (CR) or partial response (PR)); six patients (31.6%) had a best overall response (BOR) of stable disease (SD; one with W0180 3.5 mg, two with W0180 300 mg and three with W0180 600 mg) and 13 patients had a BOR of progressive disease. Of the patients with SD, four had progressive disease at their final assessment (Days 85, 106, 126 and 254) and two had SD (Days 51 and 386). One patient (in the W0180 600 mg dose-level cohort, with appendix cancer) had prolonged SD for 386 days (>12 months, last assessment). This patient had three prior lines of treatment, including chemotherapy and anti-VEGF treatment. In total, seven of the eight patients in the monotherapy arm who received treatment with PD-1/PD-L1 therapy during the study had response data available, of whom three had a BOR of SD and four of progressive disease. All patients discontinued monotherapy treatment with W0180 during the study, due to disease progression/no clinical benefit (n=15), AEs (n=2) or protocol deviation/withdrawal of consent (n=2).

In the combination therapy arm (n=9), no patients achieved objective response, three patients (33.3%) had a BOR of SD (one with W0180 60 mg+pembrolizumab and two with W0180 300 mg+pembrolizumab), and six patients had a BOR of progressive disease. Of the three patients with a BOR of SD, one had progressive disease at their final assessment (Day 81) and two had SD at their final assessment (Day 127 and Day 403 (>13 months)). The patient with the most prolonged SD (in the W0180 300 mg+pembrolizumab dose-level cohort, with squamous cell carcinoma) had received five prior lines of treatment including chemotherapy, anti-epidermal growth factor receptor, anti-PD-L1 and investigational treatments. All

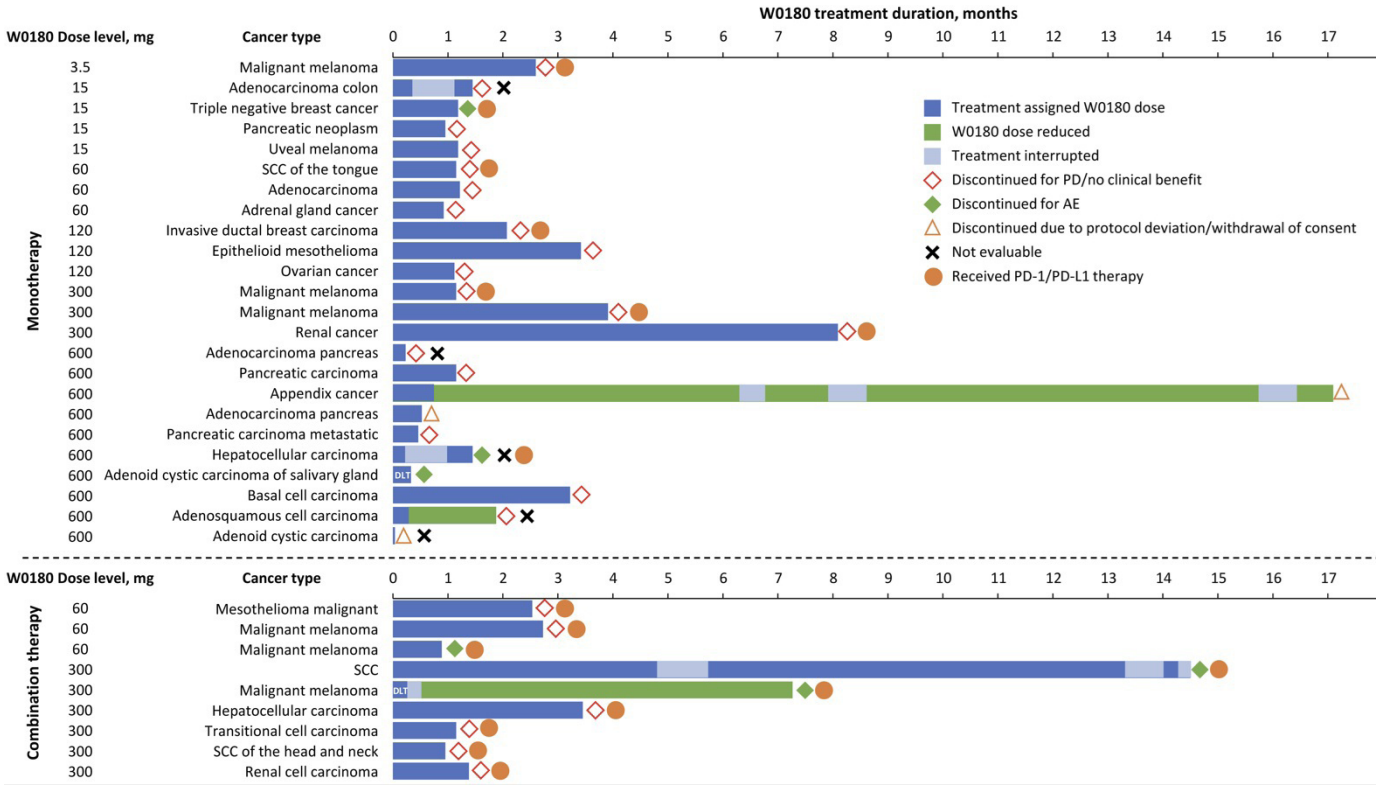

Figure 1 Swimmer plot of response to W0180 administration in patients. AE, adverse event; DLT, dose-limiting toxicity; PD, progressive disease; PD-1, programmed cell death protein-1; PD-L1, programmed death ligand-1; SCC, squamous cell carcinoma.

patients in the combination therapy arm discontinued treatment during the study, due to disease progression/no clinical benefit (n=6) or AEs (n=3).

W0180 pharmacokinetic/immunogenicity profile

After intravenous administration of W0180 as monotherapy, the maximum serum W0180 concentration ranged from 0.288 ng/mL after administration of 3.5 mg (n=1) to 106 ng/mL after administration of 600 mg (n=9; table 3). W0180 exhibited rapid clearance and showed no accumulation with repeated weekly administration (ie, was not detected in serum prior to subsequent infusion). There was a non-linear increase in exposure (area under the serum concentration-time curve and maximum serum concentration) with increased W0180 dose, with the mean experimental half-life increasing from 4.66 hours at 60 mg to 17.7 hours at 600 mg. No relationship between

Table 3 Mean pharmacokinetic parameters of W0180 after first administration

	W0180 monotherapy						Combination therapy	
	3.5 mg (n=1)	15 mg (n=4)	60 mg (n=3)	120 mg (n=3)	300 mg (n=3)	600 mg (n=9)	60 mg (n=3)	300 mg (n=6)
C_{max}, ng/mL	0.288	3.12	7.75*	NC†	81.4*	106‡	14.9*	79.4§
AUC_{0-t}, h ng/mL	0.159	6.59	70.5	449	1650	3460	90.6	1460
$AUC_{0-\infty}$, h ng/mL	NC¶	NC¶	75.7*	NC¶	1680	2940**	119††	2460‡
$t_{½}$, h	NC¶	NC¶	4.66*	NC¶	9.05	17.7**	3.91††	11.8‡
CL_{tot}, L/H	NC¶	NC¶	0.848*	NC¶	0.179	0.216**	0.504††	0.148‡

*n=2.
†Not reported because all patients had infusion durations that deviate from the anticipated length.
‡n=3.
§n=5.
¶Not calculable because no sufficient values in the elimination phase to compute terminal slope.
**n=4.
††n=1.
$AUC_{0-\infty}$, area under the serum concentration–time curve from zero to infinity; AUC_{0-t}, area under the serum concentration–time curve from zero to last quantifiable point; CL_{tot}, total clearance; C_{max}, maximum serum concentration; NC, not calculable; $t_{½}$, experimental half-life.

pharmacokinetic parameters and patient body weight was observed (data not shown).

ADAs against W0180 were identified in three patients; these ADAs had no identifiable impact on patient safety or the pharmacokinetic profile of W0180.

W0180 pharmacodynamics

One week after the first administration of W0180 as monotherapy or combination therapy (between Days 1 and 8 of Cycle 1), an increase in proliferative (Ki67+) CD4+ and CD8+ T cells and proliferative cytotoxic (Ki67+granzyme B-expressing (GZMB+)) CD4+ and CD8+ T cells was observed in 18 and 21 out of 30 patient samples of peripheral blood, respectively (online supplemental figure S6). Higher doses of W0180 (≥300 mg) were associated with significant increases from baseline in proliferative CD4+ and CD8+ T cells and proliferative cytotoxic CD4+ and CD8+ T cells. The magnitude of the increases in proliferative CD4+ or CD8+ T cells and proliferative cytotoxic CD4+ or CD8+ T cells was similar across both the monotherapy and combination therapy arms.

There was a trend towards an increase in non-classical monocytes (CD14+/CD16+) and activated NK cells (CD3−/CD56dim/CD16+/CD137+) at 1 week after the first infusion, regardless of W0180 dose (online supplemental figure S7).

Of the pro-inflammatory cytokine and chemokine biomarkers assessed, an early (end of infusion and 4 hours after the first W0180 administration) and transient increase was observed in IFN-γ, TNF-α, IL-6, IL-8, CXCL10 (IP10), MIP1-α, MIP1-β and MCP-1 (online supplemental figure S8). No change versus baseline in Cycle 1, Day 2 pre-dose was observed at 1 week after the first infusion (data not shown).

Paired biopsies at baseline and on-treatment (available for 16 patients) showed an increase in TILs in 10 patients (figure 2); however, this increase was not dose-related nor correlated with VISTA expression at baseline (VISTA H-score or VISTA+cell density; online supplemental figure S9).

Based on baseline tumour biopsies, retrospective analysis shows the majority of patients in the FAS had low VISTA expression (online supplemental table S5). Only five patients out of 25 analysed had high VISTA expression (H-Score >10), seven had high PD-L1 expression (CPS >5%) and one had high expression of both VISTA and PD-L1. No correlation was found between VISTA expression at baseline (H-Score or VISTA+cell density) and clinical response (duration in the study; online supplemental figure S9). A concise overview of the biological properties of W0180 is provided in the graphical abstract (online supplemental file 3).

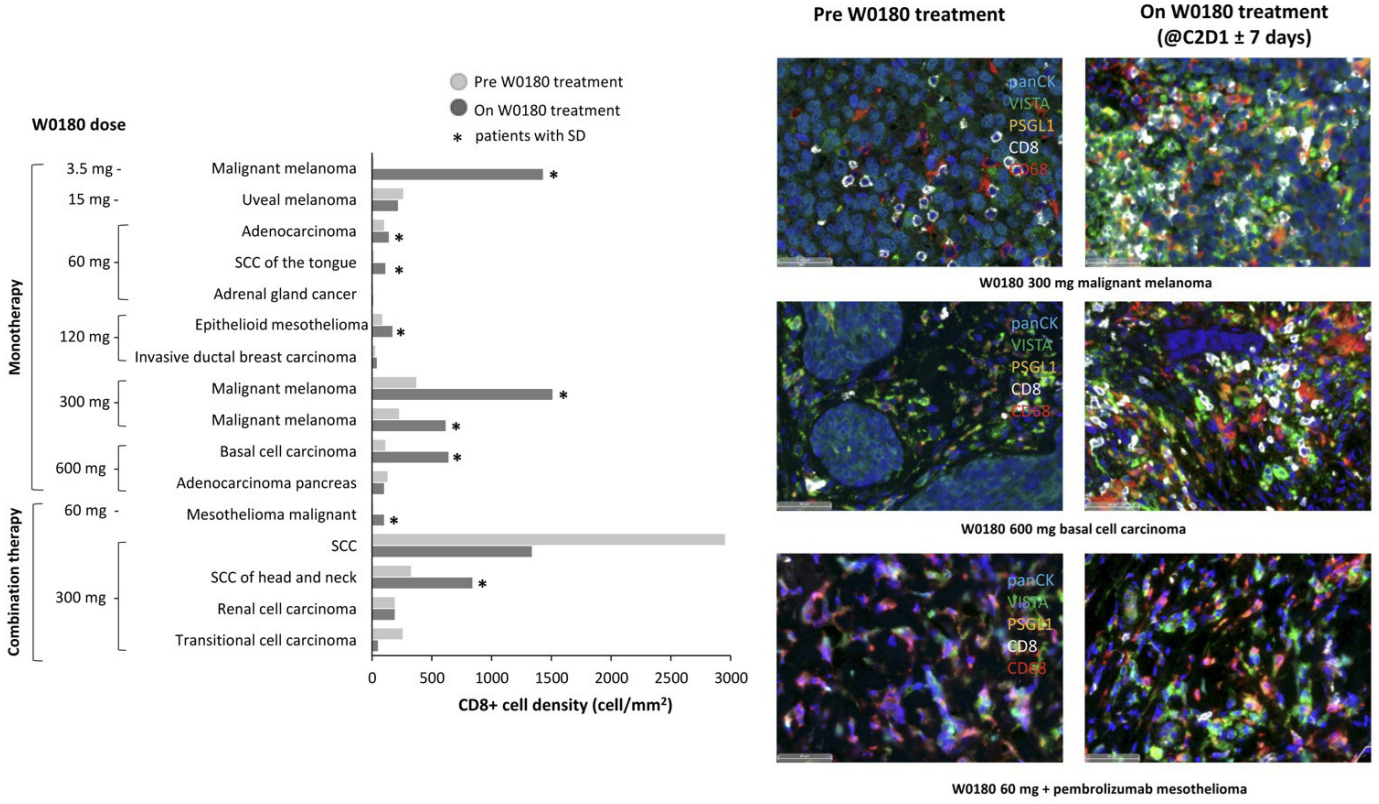

Figure 2 Tumour infiltrating lymphocyte (CD8+) T-cell density in paired biopsies, determined by counting the positive CD8+ cells in stained slides of biopsies collected before Cycle 1, Day 1 dose of W0180 (baseline) and on W0180 treatment (Cycle 2, Day 1±7 days). C, cycle; D, day; panCK, pan-cytokeratin; PSGL1, P-selectin glycoprotein ligand-1; SCC, squamous cell carcinoma; SD, stable disease; VISTA, V domain-containing immunoglobulin suppressor of T-cell activation.

DISCUSSION

In this first-in-human study conducted in patients with locally advanced or metastatic solid tumours, W0180 was associated with a manageable safety profile. However, two DLTs were reported (cerebral infarction and IRR). The MTD/RDE was not reached as the study was discontinued earlier than planned by the sponsor. Although the safety profile of W0180 was manageable, almost all patients experienced an IRR during treatment. Most IRRs were of mild severity (ie, Grade 1–2); however, four patients (14.3%) had Grade ≥3 IRRs. Given the lack of systematic and consistent IRR prophylaxis during the study conduct, no clear conclusions can be drawn regarding IRR risk, which requires further evaluation with a more homogenous approach.

Exposure to W0180 as monotherapy or in combination with pembrolizumab was short, with most patients discontinuing treatment within the first few treatment cycles due to disease progression. No objective response was observed with monotherapy or combination therapy; however, two patients had prolonged SD for >12 months (one from each treatment arm).

In this study, W0180 exhibited non-linear pharmacokinetics up to the highest dose administered in the clinical study (ie, 600 mg). Non-linear pharmacokinetics is a common phenomenon for monoclonal antibodies and is due to a phenomenon known as target mediated drug disposition (TMDD): elimination of the drug is dependent on its target binding. Even at the highest dose tested (600 mg QW), preclinical modelling suggested that VISTA is not fully occupied over the whole therapeutic interval (ie, 168 hours)[15]; therefore, TMDD was not saturated, which explains the non-linear pharmacokinetics observed in our study.

In our preclinical experiments, W0180 exhibited pH-independent blockade of VISTA interaction with its main ligands and induced monocyte activation in vitro. In vivo, W0180 demonstrated antitumour activity as monotherapy and in combination with anti-PD-1 therapy in a syngeneic preclinical murine model of cancer. Among the multiple cell populations analysed by immunophenotyping during Cycle 1 of our first-in-human study, the greatest changes were observed for proliferative and proliferative cytotoxic CD8+ and CD4+ T cells at the highest W0180 doses in both the monotherapy and combination therapy arms. Interestingly, this pharmacodynamic response was observed 1 week post infusion, even in cases where the pharmacokinetic profile showed no W0180 detection at this time point. At 1 week post W0180 infusion, no increase of activated monocytes was observed in the first-in-human study (despite this being shown in preclinical models), and only a trend to increased activated NK at the highest doses was seen.

Despite the rapid and transient increase in pro-inflammatory cytokines and chemokines related to T-cell and monocyte activation in blood observed with W0180 administration in this first-in-human study, these changes did not appear to be sufficient to induce antitumour activity. These results, as well as the absence of a robust effectiveness signal, raise important questions around our understanding of the complex biology of this target at the peripheral level but also in the context of the TME. Furthermore, evaluation of paired tumour biopsies showed an increase in TIL density in the TME for 10 out of 16 patients, suggesting a pharmacodynamic effect of W0180; however, the low number of paired biopsies analysed, combined with the heterogeneity of the patients, variable TIL density and unexpected low target expression at baseline, makes the interpretation of tumour biomarker data somewhat complex.

As none of the patients achieved objective response in the first-in-human study, it was not possible to identify robust predictive markers of response. No correlation was found between VISTA expression at baseline and clinical response (number of cycles in the study) but data on expression were limited (available for 25 patients of whom five had high VISTA expression). However, several anti-VISTA monoclonal antibodies are currently being developed for the treatment of cancer,[19] including onvatilimab (CI-8993; JNJ-61610588), KVA12123 and SNS-101.[20–23] Although W0180 was associated with IRRs, these were generally mild in severity and manageable. Therefore, the findings of this first-in-human study of W0180, in addition to the ongoing clinical studies of other anti-VISTA antibodies, provide rationale for continued development of VISTA inhibitors for the treatment of cancer. In future studies, prospective selection of patients will be needed based, at least, on tumour VISTA and PD-L1 expression levels on TILs and tumour cells, as anti-VISTA antibodies appear to enhance the antitumour activity of anti-PD(L)-1 therapies.

The limitations of this study included the heterogeneous study population and the retrospective analysis of tumour biopsies, which showed unexpected low levels of VISTA and PD-L1 expression. Most of the patients included had metastatic lesions rather than primary tumours, which may explain the poor TIL density at baseline and low VISTA expression.[24] In addition, the study was terminated early before the RDE could be assessed, while the pharmacokinetic profile remained non-linear between doses of 300 and 600 mg, which suggests that full VISTA occupancy was not achieved. Pharmacodynamic data suggest that these two high doses appear to be close to the active dose.

CONCLUSIONS

W0180 demonstrated pH-independent VISTA inhibition in vitro and improved antitumour activity in vivo when administered in combination with an anti-PD-1 antibody. In the first-in-human clinical study, W0180 demonstrated dose-dependent pharmacodynamic activity in peripheral blood and tumours, as well as manageable safety in patients with locally advanced or metastatic solid tumours.

Author affiliations
[1]Department of Medical Oncology & Clinical Research Unit, Oncopole Claudius Regaud, IUCT-Oncopole, University of Toulouse, Toulouse, France

[2]Département d'Innovation Thérapeutique et d'Essais Précoces (DITEP), Gustave Roussy Institute, Villejuif, France
[3]Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA
[4]Clinica Universidad de Navarra, Madrid, Spain
[5]Medical Oncology, Centre Léon Bérard, Lyon, France
[6]Pierre Fabre Laboratories, Castres, France
[7]CUN, CIMA and CIBERONC, Universidad de Navarra, Pamplona, Spain
[8]Nuffield Department of Medicine, University of Oxford, Oxford, UK

Acknowledgements We would like to thank Eric Chetaille, Pierre Ferre, Maria Pavlyuk and Francisco Cruzalegui for assistance in the conception and design of the study; Hatem Azim, Christine Wilkinson Blanc, Bérengère Jean and Ana Catarina Pinto for providing operational follow-up of the clinical trial; Alain Beck and Carole Georgeon-Chartier for the compound supply; Grégoire Zorza and Frédéric Ausseil for translational clinical activities; Isabelle Vandenberghe, Matthieu Broussas, Elise Bonotto, Olivier Delfour, Yannick Leveque, Sylvain Meriau and Pierre Launay for data collection, visualization and analysis; Noureddine Loukili, Nicolas Boute and Nathalie Corvaia for their assistance in the preclinical studies; Frederique Lafforgue for project management; Florence Cardona Giordano, Mathias Domostoj, Charlotte Lacroix, Delphine Allain, Camille Diebold Chatillon and Laurence Castillo Morellato for safety management; and Sarah Greig, PhD, CMPP, of Springer Health+ who provided medical writing assistance in the development of the outline and subsequent drafts of the manuscript and Kate Palmer, also of Springer Health+, who assisted with post-submission revisions. The medical writing assistance was funded by Pierre Fabre Laboratories.

Contributors AM is the guarantor. Preclinical experiment design, protocol writing and amendments: AM, DJ, MP and GG-D; Investigation and enrolment of the patients: AM, CG-R, SC, FXD, EC, PAC and IM; Contribution to data assembly, analysis and interpretation: MP, ED, AP, DJ, MS, GG-D and CF. CF accepts full responsibility for the finished work and/or the conduct of the study, had access to the data and controlled the decision to publish. All authors discussed the results and contributed to the final manuscript.

Funding This study, development of the manuscript and article processing charge fee were funded by Les Laboratories Pierre Fabre. Les Laboratories Pierre Fabre was involved in the study design; data collection, analysis and interpretation; study report writing; and the decision to submit this paper for publication.

Competing interests CG-R has received honoraria from Bristol Myers Squibb, Eisai, Ellipses Pharma, Foundation Medicine, Genentech Roche, Macomics and Pierre Fabre; has received research funding from Amgen, Bristol Myers Squibb and Genentech/Roche; has received travel funding from Genentech/Roche, MSD Oncology and Pierre Fabre; and has acted in a consulting or advisory role for Bristol Myers Squibb. SC has received honouraria from Amgen, AstraZeneca, Bristol Myers Squibb, Eisai, Fresenius Kabi, Genmab, Janssen, Merck, MSD, Novartis and Roche; has received travel funding from Amgen, AstraZeneca, Bristol Myers Squibb and Roche; and has acted in a consulting or advisory role for Amgen, Alderaan Biotech, AstraZeneca, Avacta Life Sciences, Celanese, Domain Therapeutics, Ellipses Pharma, Immunicom, Nanobiotix, NextCure, Oncovita, Seattle Genetics, Tatum Bioscience, Tollys SAS and UltraHuman. FXD and EC have no conflicts of interest to declare. PAC has received a grant from Amgen and EMD Serono. ED, DJ, MP, AP, MS, GG-D and CF are employees of Pierre Fabre Laboratories. AM provided scientific and medical consulting services to Pierre Fabre during the preparation of the protocol for the trial; has received travel funding from Bristol Myers Squibb, Roche/Genentech, Incyte and MSD; has acted in a consulting or advisory role for Adagene, AstraZeneca, BioLineRx, Centessa Pharmaceuticals, Clover Biopharmaceuticals, Deka Biosciences, Depth Charge Therapeutics, Eisai, Gray Wolf Therapeutics, Gritstone Bio, Guidepoint Global, HiFiBiO Therapeutics, Hotspot Therapeutics, Innate Pharma, ImCheck therapeutics, Johnson & Johnson/Janssen, Lytix Biopharma, Medicxi, MSD, Neogene Therapeutics, OSE Immunotherapeutics, PegaOne, Pierre Fabre, Roche, Redx Pharma, Sanofi, Servier, Shattuck Labs, Sotio and Third Rock Ventures; has stock or ownership in Centessa Pharmaceuticals, Deka Biosciences, HotSpot Therapeutics, Marengo and Shattuck Labs; and has a patent for monoclonal antibodies against CD81 (Stanford University). IM has received research funding from Alligator Bioscience, Bioncotech, Bristol Myers Squibb and Roche/Genentech; has received travel funding from Bristol Myers Squibb, Incyte, MSD and Roche/Genentech; and has acted in a consulting or advisory role for AstraZeneca/MedImmune, Boston Pharma, Bristol Myers Squibb, Bayer, CatalYm, CRISPR Therapeutics, MSD, EMD Serono, F-star, Genmab, Gossamer Bio, Lilly, Moderna Therapeutics and Monopteros Therapeutics, Noxxon Pharma, Numab, Pieris Pharma, Roche/Genentech, Servier and Tusk Therapeutics.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved. The first-in-human study (EudraCT: 2019-002299-15) was conducted in accordance with the study protocol approved by institutional review boards/independent ethics committees, as well as the ethical principles derived from the Declaration of Helsinki, applicable International Council of Harmonisation Good Clinical Practice guidelines, and all applicable laws and regulations. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The datasets used and/or analysed during the current study are available from CF (claire.fabre@pierre-fabre.com) or GG-D (genevieve.gueguen-dorbes@pierre-fabre.com) on reasonable request. The full trial protocol is available in the online supplementary material.

ORCID iDs
Philippe Alexandre Cassier https://orcid.org/0000-0003-3857-1688
Aurélien Marabelle https://orcid.org/0000-0002-5816-3019
Ignacio Melero https://orcid.org/0000-0002-1360-348X

REFERENCES

1 Wang L, Rubinstein R, Lines JL, *et al*. VISTA, a novel mouse Ig superfamily ligand that negatively regulates T cell responses. *J Exp Med* 2011;208:577–92.
2 Wang J, Wu G, Manick B, *et al*. VSIG-3 as a ligand of VISTA inhibits human T-cell function. *Immunology* 2019;156:74–85.
3 Blando J, Sharma A, Higa MG, *et al*. Comparison of immune infiltrates in melanoma and pancreatic cancer highlights VISTA as a potential target in pancreatic cancer. *Proc Natl Acad Sci U S A* 2019;116:1692–7.
4 Lines JL, Pantazi E, Mak J, *et al*. VISTA is an immune checkpoint molecule for human T cells. *Cancer Res* 2014;74:1924–32.
5 Rabadi D, Sajani AA, Noelle RJ, *et al*. The role of VISTA in the tumor microenvironment. *J Cancer Metastasis Treat* 2022;8:24.
6 Yuan L, Tatineni J, Mahoney KM, *et al*. VISTA: A Mediator of Quiescence and a Promising Target in Cancer Immunotherapy. *Trends Immunol* 2021;42:209–27.
7 Shekari N, Shanehbandi D, Kazemi T, *et al*. VISTA and its ligands: the next generation of promising therapeutic targets in immunotherapy. *Cancer Cell Int* 2023;23:265.
8 Flies DB, Han X, Higuchi T. T cell-mediated immunity. *J Clin Invest* 2014;124:1966–75.
9 Wang L, Le Mercier I, Putra J, *et al*. Disruption of the immune-checkpoint *VISTA* gene imparts a proinflammatory phenotype with predisposition to the development of autoimmunity. *Proc Natl Acad Sci USA* 2014;111:14846–51.
10 Liu J, Yuan Y, Chen W, *et al*. Immune-checkpoint proteins VISTA and PD-1 nonredundantly regulate murine T-cell responses. *Proc Natl Acad Sci USA* 2015;112:6682–7.
11 ElTanbouly MA, Schaafsma E, Noelle RJ, *et al*. VISTA: Coming of age as a multi-lineage immune checkpoint. *Clin Exp Immunol* 2020;200:120–30.
12 Gao J, Ward JF, Pettaway CA, *et al*. VISTA is an inhibitory immune checkpoint that is increased after ipilimumab therapy in patients with prostate cancer. *Nat Med* 2017;23:551–5.

13 Kakavand H, Jackett LA, Menzies AM, *et al*. Negative immune checkpoint regulation by VISTA: a mechanism of acquired resistance to anti-PD-1 therapy in metastatic melanoma patients. *Mod Pathol* 2017;30:1666–76.
14 Mulati K, Hamanishi J, Matsumura N, *et al*. VISTA expressed in tumour cells regulates T cell function. *Br J Cancer* 2019;120:115–27.
15 Loukili N, Vandenberghe I, Delfour O, *et al*. Abstract 2400: K01401-020 is a novel anti-VISTA antibody for cancer treatment: Pharmacodynamic impact on non-human primates and human immune system. *Cancer Res* 2019;79:2400.
16 Schwartz LH, Litière S, de Vries E, *et al*. RECIST 1.1-Update and clarification: From the RECIST committee. *Eur J Cancer* 2016;62:132–7.
17 Seymour L, Bogaerts J, Perrone A, *et al*. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. *Lancet Oncol* 2017;18:e143–52.
18 Navarro-Fontestad C, González-Álvarez I, Fernández-Teruel C, *et al*. A new mathematical approach for the estimation of the AUC and its variability under different experimental designs in preclinical studies. *Pharm Stat* 2012;11:14–23.
19 Wu C, Cao X, Zhang X. VISTA inhibitors in cancer immunotherapy: a short perspective on recent progresses. *RSC Med Chem* 2021;12:1672–9.
20 Iadonato S, Ovechkina Y, Lustig K, *et al*. A highly potent anti-VISTA antibody KVA12123 - a new immune checkpoint inhibitor and a promising therapy against poorly immunogenic tumors. *Front Immunol* 2023;14:1311658.
21 Noelle R, Johnson M, Rodon J, *et al*. 761 Pharmacokinetic and pharmacodynamic data from a phase 1 study of ci-8993 anti-vista antibody in patients with advanced solid tumors. SITC 37th Annual Meeting (SITC 2022) Abstracts; November 2022:A793.
22 Thisted T, Mukherjee A, Malhotra K, *et al*. 228 Antagonistic ph-selective vista antibody sns-101 potentiates anti-pd-1/pd-l1-induced anti-tumor immunity. SITC 36th Anniversary Annual Meeting (SITC 2021) Abstracts; November 2021:A243.
23 Sen S, Call JA, Papadopoulos KP, *et al*. Initial results from a first-in-human phase 1 study of SNS-101 (pH-selective anti-VISTA antibody) alone or in combination with cemiplimab in patients with advanced solid tumors. *JCO* 2024;42:2600.
24 Bredel D, Tihic E, Mouraud S, *et al*. Immune checkpoints are predominantly co-expressed by clonally expanded CD4+FoxP3+ intratumoral T-cells in primary human cancers. *J Exp Clin Cancer Res* 2023;42:333.