IPH4102, a first-in-class anti-KIR3DL2 monoclonal antibody, in patients with relapsed or refractory cutaneous T-cell lymphoma: an international, first-in-human, open-label, phase 1 trial

Martine Bagot, Pierluigi Porcu, Anne Marie-Cardine, Maxime Battistella, Basem M William, Maarten Vermeer, Sean Whittaker, Federico Rotolo, Caroline Ram-Wolff, Michael S Khodadoust, Armand Bensussan, Carine Paturel, Cecile Bonnafous, Helene Sicard, Hatem A Azim Jr, Youn H Kim

Summary

Background IPH4102 is a first-in-class monoclonal antibody targeting KIR3DL2, a cell surface protein that is expressed in cutaneous T-cell lymphoma, and predominantly in its leukaemic form, Sézary syndrome. We aimed to assess the safety and activity of IPH4102 in cutaneous T-cell lymphoma.

Methods We did an international, first-in-human, open-label, phase 1 clinical trial with dose-escalation and cohort-expansion parts in five academic hospitals in the USA, France, the UK, and the Netherlands. Eligible patients had histologically confirmed relapsed or refractory primary cutaneous T-cell lymphoma, an Eastern Cooperative Oncology group performance score of 2 or less, were aged 18 years or older, and had received at least two previous systemic therapies. Ten dose levels of IPH4102, administered as an intravenous infusion, ranging from 0·0001 mg/kg to 10 mg/kg, were assessed using an accelerated 3+3 design. The primary endpoint was the occurrence of dose-limiting toxicities during the first 2 weeks of treatment, defined as toxicity grade 3 or worse lasting for 8 or more days, except for lymphopenia. Global overall response by cutaneous T-cell lymphoma subtype was a secondary endpoint. Safety and activity analyses were done in the per-protocol population. The study is ongoing and recruitment is complete. This trial is registered with ClinicalTrials.gov, number NCT02593045.

Findings Between Nov 4, 2015, and Nov 20, 2017, 44 patients were enrolled. 35 (80%) patients had Sézary syndrome, eight (18%) had mycosis fungoides, and one (2%) had primary cutaneous T-cell lymphoma, not otherwise specified. In the dose-escalation part, no dose limiting toxicity was reported and the trial's safety committee recommended a flat dose of 750 mg for the cohort-expansion, corresponding to the maximum administered dose. The most common adverse events were peripheral oedema (12 [27%] of 44 patients) and fatigue (nine [20%]), all of which were grade 1–2. Lymphopenia was the most common grade 3 or worse adverse event (three [7%]). One patient developed possibly treatment-related fulminant hepatitis 6 weeks after IPH4102 discontinuation and subsequently died. However, the patient had evidence of human herpes virus-6B infection. Median follow-up was 14·1 months (IQR 11·3–20·5). A confirmed global overall response was achieved in 16 (36·4% [95% CI 23·8–51·1]) of 44 patients, and of those, 15 responses were observed in 35 patients with Sézary syndrome (43% [28·0–59·1]).

Interpretation IPH4102 is safe and shows encouraging clinical activity in patients with relapsed or refractory cutaneous T-cell lymphoma, particularly those with Sézary syndrome. If confirmed in future trials, IPH4102 could become a novel treatment option for these patients. A multi-cohort, phase 2 trial (TELLOMAK) is underway to confirm the activity in patients with Sézary syndrome and explore the role of IPH4102 in other subtypes of T-cell lymphomas that express KIR3DL2.

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Hôpital Saint Louis, Paris, France (Prof M Bagot MD, M Battistella MD, C Ram-Wolff MD); **INSERM U976, Paris 7 University, Paris, France** (Prof M Bagot, A Marie-Cardine PhD, M Battistella, C Ram-Wolff, A Bensussan PhD); **Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA, USA** (Prof P Porcu MD); **The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA** (B M William MD); **Leiden University Medical Center, Leiden, Netherlands** (Prof M Vermeer MD); **Guy's and St Thomas' Hospital, London, UK** (Prof S Whittaker MD); **Innate Pharma, Marseille, France** (F Rotolo PhD, C Paturel PhD, C Bonnafous PhD, H Sicard PhD, H A Azim Jr MD); **and Stanford Cancer Institute, Stanford, CA, USA** (M S Khodadoust MD, Prof Y H Kim MD)

Correspondence to:
Prof Martine Bagot, Hôpital Saint Louis, 75010 Paris, France
martine.bagot@aphp.fr

Introduction

Cutaneous T-cell lymphomas are a heterogeneous group of rare, extranodal, non-Hodgkin lymphomas, with approximately 3000 new cases diagnosed in the USA every year.[1] The most common subtype of cutaneous T-cell lymphoma is mycosis fungoides, which accounts for 50–60% of all cases.[2] Sézary syndrome is a rare, leukaemic subtype that is characterised by erythroderma, lymphadenopathy, and high burden of neoplastic T cells (Sézary cells) in the blood.[3] Patients with Sézary syndrome typically have severe pruritus, frequent infections, and body disfigurement resulting in poor quality of life.[4] Prognosis is dismal, with median survival ranging from 2·5 to 4 years.[5,6]

On the basis of the results of two randomised trials, brentuximab vedotin and mogamulizumab were

Research in context

Evidence before this study

We searched the scientific literature to identify reports of patients with cutaneous T-cell lymphoma, Sézary syndrome, and KIR3DL2. We searched Medline for studies published in English from Jan 1, 1990, to Dec 31, 2018. Search items included "cutaneous T-cell lymphoma", "KIR3DL2", and "Sézary syndrome". Cutaneous T-cell lymphoma is an uncommon and incurable form of non-Hodgkin lymphoma. Sézary syndrome accounts for around 5–10% of cutaneous T-cell lymphomas and is the leukaemic and most aggressive form, with median survival rarely exceeding 4 years. Affected patients typically have severe pruritus, frequent infections, and body disfigurement resulting in poor quality of life. In 2018, two novel drugs, brentuximab vedotin and mogamulizumab, were approved for the treatment of subsets of patients with cutaneous T-cell lymphoma who received at least one previous systemic therapy. However, patients with Sézary syndrome were included only in the trial of mogamulizumab. In more refractory patients (ie, those who have received at least two prior systemic therapies), no drugs are proven to be effective in patients with Sézary syndrome. Vorinostat is the only approved agent in the USA, which in a phase 3 trial showed an overall response of 2% in patients with Sézary syndrome. KIR3DL2 (CD158k) is a member of the highly polymorphic family of killer-cell immunoglobulin-like receptors and is widely expressed in cutaneous T-cell lymphoma, and in more than 85% of patients with Sézary syndrome, and was proposed as the most sensitive diagnostic and prognostic marker for these patients.

Added value of this study

To our knowledge, this study is the first reported trial of the anti-KIR3DL2 antibody IPH4102. We report activity of this novel, targeted drug in a rare form of cutaneous T-cell lymphoma, Sézary syndrome, with a high unmet medical need. Unlike previous studies of drugs in patients with refractory cutaneous T-cell lymphoma who received at least two previous systemic therapies, this study used the international consensus response criteria. This study shows high activity of IPH4102 in patients with Sézary syndrome who received at least two previous systemic therapies. The treatment was well tolerated with no identified dose-limiting toxicity. These results represent a potential new treatment for patients with refractory Sézary syndrome.

Implications of all the available evidence

On the basis of our results, IPH4102 received fast-track designation from the US Food and Drug Administration for the treatment of adult patients with relapsed or refractory Sézary syndrome who have received at least two prior systemic therapies . A multi-cohort phase 2 trial (TELLOMAK) is underway to confirm the activity in patients with Sézary syndrome and explore the role of IPH4102 in other subtypes of T-cell lymphomas that express KIR3DL2.

approved for the treatment of subsets of patients with cutaneous T-cell lymphoma who received at least one prior systemic therapy.[7,8] Only the trial with mogamulizumab included patients with Sézary syndrome. In more refractory patients (ie, those who have received at least two prior systemic therapies), vorinostat is the only approved agent in the USA with modest clinical activity in patients with Sézary syndrome.[8] Notably, no agents are approved in Europe for such patients.

See Online for appendix

KIR3DL2 (CD158k) is a member of the highly polymorphic family of killer-cell immunoglobulin-like receptors and is widely expressed in cutaneous T-cell lymphoma; it is expressed in more than 85% of patients with Sézary syndrome.[9] KIR3DL2 was proposed as the most sensitive diagnostic and prognostic marker for Sézary syndrome,[10] suggesting that it could serve as an ideal therapeutic target for these patients.

IPH4102 is a humanised, first-in-class, monoclonal antibody that is designed to deplete KIR3DL2-expressing cells via antibody-dependent cell cytotoxicity and phagocytosis.[11] The drug has shown anti-tumour activity in mouse xenograft models and ex-vivo autologous assays using patient-derived natural killer cells and Sézary cells.[11] We report the results of the first-in-human, phase 1 study assessing IPH4102 in patients with relapsed or refractory cutaneous T-cell lymphoma.

Methods

Study design and participants

We did an international, first-in-human, open-label, phase 1 study in five academic hospitals in the USA, France, the UK, and the Netherlands (appendix p 2). The study was composed of dose-escalation and cohort-expansion portions and was done in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The study protocol was approved by the institutional review board at each participating site and is included in the appendix. All patients provided signed informed consent before being screened for enrolment.

Eligible patients had histologically confirmed primary cutaneous T-cell lymphoma that was relapsed or refractory, were aged 18 years or older, had received at least two previous systemic therapies, and had an Eastern Cooperative Oncology group performance score of 2 or less. In the dose-escalation part, based on scientific advice from the European Medicines Agency on Nov 20, 2014, only patients who had at least 5% of infiltrating mononuclear cells expressing KIR3DL2 in the skin or 5% phenotypically aberrant circulating T cells expressing KIR3DL2 were included. Two expansion cohorts were planned in the two cutaneous T-cell lymphoma subtypes known to express KIR3DL2 in most

patients,[9] Sézary syndrome and mycosis fungoides with evidence of large-cell transformation, with a target recruitment of 15 patients in each cohort. The protocol was amended in March 23, 2017, to allow recruitment of patients irrespective of KIR3DL2 expression in the cohort-expansion part. Further details of inclusion and exclusion criteria are provided in the appendix (p 3).

A safety data monitoring committee that comprised study investigators and representatives from the sponsor convened at regular intervals to overview the safety of trial participants and inform on dose-escalation decisions, declaration of dose-limiting toxicities, the maximum tolerated dose, and the recommended phase 2 dose.

Procedures

In the dose-escalation part, an accelerated 3+3 design was used to identify the maximum tolerated dose.[12] One patient was treated at each of the first three dose levels, and subsequently three patients were treated per dose level until the maximum administered dose of 10 mg/kg was reached. The first tested dose was 0·0001 mg/kg and intra-patient dose escalation was allowed (figure 1). In the cohort expansion part, all patients were treated with the recommended dose as based on the results of the dose-escalation part. Treatment was a 1 h intravenous infusion administered weekly for the first month, every 2 weeks for the following ten administrations, and then every 4 weeks until disease progression or unacceptable toxicity. No dose reductions were allowed. Dose interruption due to an adverse event was allowed for up to a maximum of 4 weeks as judged by the investigator. The protocol recommended permanent discontinuation of IPH4102 in case of severe infusion-related reaction, unresolved grade 3 liver toxicity, or other adverse events requiring discontinuation according to the investigator's assessment.

Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).[13] Dose-limiting toxicities were defined as adverse events of grade 3 or worse lasting for 8 or more days, except lymphopenia. Maximum tolerated dose was defined as the highest dose level where none out of three or no more than one out of six patients had a dose-limiting toxicity within 14 days after first IPH4102 administration.

Overall response was assessed using the global composite response score based on response in the different compartments—skin, blood, lymph nodes, and viscera—as described in the international consensus criteria (appendix p 5).[14] Response was assessed between the first administered dose and the end of treatment. To have a best global response, patients had to have a confirmatory response assessment no sooner than 4 weeks after the initial documentation of response.[14] Skin response was assessed using the modified Severity Weighted Assessment Tool.[15] In the dose-escalation part, either flow cytometry or cytomorphology was used to assess blood response as per the investigator's preference. In the cohort expansion part, only flow cytometry was used for blood response. Skin and blood compartments were assessed every 4 weeks. Lymph node and visceral involvement were assessed at baseline using MRI, CT, or PET at the discretion of the investigator. If positive, follow-up imaging was done at week 5 and then every 12 weeks thereafter. Quality of life was assessed on the same day as each IPH4102 infusion using Skindex-29[16] and presence and severity of pruritus was assessed using a visual analogue scale (VAS).[17] Skin biopsies were defined per protocol and were obtained at baseline, week 5, week 14, and the end of treatment.

KIR3DL2 expression was measured using an anti-KIR3DL2 antibody (for immunohistochemistry: clone 12B11, mouse IgG1 isotype [Innate Pharma, Marseille, France]; for flow cytometry: clone 13E4, mouse IgG1 isotype [Innate Pharma, Marseille, France]). Both antibodies bind to KIR3DL2 on different epitopes than IPH4102.

Detection of anti-drug antibodies was based on electrochemiluminescence using a bridging format that uses a mix of biotin-labelled IPH4102 and SULFO-TAG-labelled IPH4102 (Innate Pharma, Marseille, France).

Serum samples for pharmacokinetic analysis were taken. Maximum and trough concentration of IPH4102

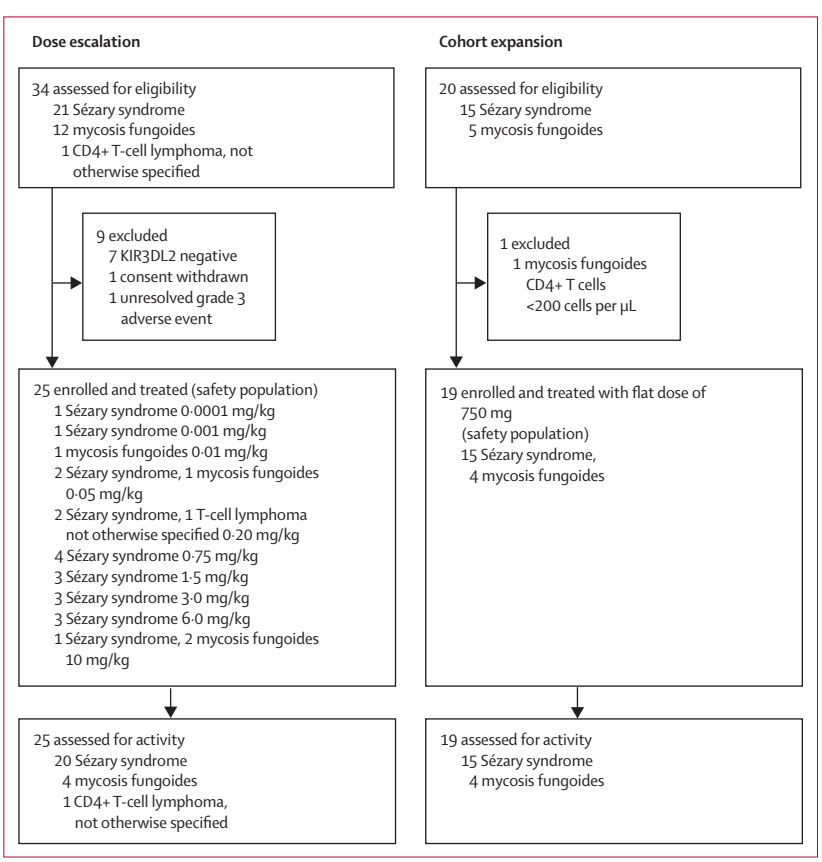

Figure 1: **Trial profile**

after administration were measured by area under the curve (AUC) from time 0 to day 7 for the first and fourth administration and accumulation index (in terms of ratio of Cmax and of AUC 0–7 days between the fourth and first administration). Immunogenicity was measured by the presence of human anti-drug antibodies before and during treatment and the neutralising potential of existing or developing anti-drug antibodies. Characterisation of pharmacodynamics biomarkers in the skin (by immunohistochemistry) and blood (by flow cytometry) was done through the monitoring of KIR3DL2-expressing cells before and during treatment. Minimal residual disease was assessed using high-throughput sequencing of the clonal T-cell receptor rearrangements of neoplastic T cells in the skin and blood.

KIR3DL2 expression and histological assessment of large-cell transformation were done centrally at Saint Louis Hospital (Paris, France). Pharmacokinetics and immunogenicity, immunohistochemistry, and the detection of minimal residual disease were done by Quality Assistance (Donstiennes, Belgium), Histalim (Montpellier, France), and Adaptive Biotechnologies (Seattle, WA, USA), respectively, under the paid supervision of the sponsor. Immunomonitoring was done centrally at Saint Louis Hospital for European sites and in the USA at ABL (Rockville, MD, USA) during the dose-escalation and at Caprion Biosciences (Montreal, QC, Canada) during the cohort expansion.

Outcomes

The primary endpoint was the occurrence of dose-limiting toxicities (adverse events of grade 3 or worse lasting for 8 or more days, except lymphoma) during the first 2 weeks of treatment. Secondary endpoints were global overall response (defined as the proportion of patients achieving a complete response or partial response), duration of response (defined as time from first response until disease progression), response by involved compartment, progression-free survival (defined as the time from day 1 of study treatment until the first occurrence of progressive disease, relapse, or death), pharmacokinetics, immunogenicity, and pruritus severity.

Exploratory objectives included quality of life, the characterisation of pharmacodynamic biomarkers in the skin and blood, and minimal residual disease. Other exploratory biomarker analyses that were done but will be reported elsewhere included the investigation of natural-killer cells, macrophage infiltration, other immune receptors, cytokine release, and whole-blood gene expression profiling.

Statistical analysis

In the dose-escalation part, an accelerated 3+3 design was used.[12] Cohort expansion was designed to confirm the safety of the recommended dose and investigate clinical activity without any a priori assumption regarding sample size.

Safety data were summarised for the safety population (patients who received at least one dose of IPH4102). Clinical activity analysis was done according to cutaneous T-cell lymphoma subtype (ie, Sézary syndrome or mycosis fungoides) for the activity population (patients who received at least one dose of IPH4102 and had a baseline disease assessment and at least one subsequent scheduled disease assessment).

Duration of response and progression-free survival were estimated using the Kaplan–Meier method and were censored at the latest disease assessment. We did a post-hoc analysis of response in patients with Sézary Syndrome according to the presence of large-cell transformation at baseline and previous treatment with mogamulizumab. The quality-of-life analysis is detailed in the appendix (p 5). The association between KIR3DL2 expression in skin and blood and minimal residual disease in both compartments, measured on weeks 5 and 14, and clinical activity was assessed using per protocol descriptive statistics. All statistical analyses were done using SAS (version 9.3) and R (version 3.5).

This study is registered with ClinicalTrials.gov, number NCT02593045.

Role of the funding source

The funder, Innate Pharma, and the trial safety committee members jointly designed the trial. The investigators and the funders collected and interpreted the data. Data analysis was done by the sponsor. All authors, including representatives from the sponsor, contributed to the writing of the manuscript and approved the final version for submission. MB, FR, and HAA Jr had access to the raw data. MB and YHK had final authority over the manuscript and the responsibility for the decision to submit for publication.

Results

Between Nov 4, 2015, and Nov 20, 2017, 54 patients with relapsed or refractory cutaneous T-cell lymphoma were screened; 34 for the dose-escalation part and 20 for the cohort-expansion part (figure 1). 44 patients were enrolled and received at least one dose of IPH4102; 25 in the dose-escalation part and 19 in the cohort-expansion part (figure 1). Recruitment in the cohort-expansion part was restricted because of a shortage in drug supply.

Patient characteristics are summarised in table 1. The median age was 69 years (IQR 58–76) and 35 (80%) of 44 patients had Sézary syndrome and stage IV disease. As per protocol, all patients had received at least two previous systemic therapies except for one patient with Sézary syndrome in the cohort expansion, who was documented as having a protocol violation. 17 (39%) patients received IPH4102 as the fifth line or higher of systemic therapy.

Flow cytometry assessment of patients with Sézary syndrome showed that 27 (77%) of 35 had the CD3+CD4+CD26– phenotype and seven (20%) had

the CD3+CD4+CD7– phenotype. One patient had a CD26+CD7+ phenotype in the Sézary cells, thus this patient was alternatively identified and followed up using the individual clonotypic surface T-cell receptor (Vbeta chain).

Ten dose levels of IPH4102 were investigated in the dose-escalation part, ranging from 0·0001 mg/kg to 10 mg/kg. No dose-limiting toxicities were observed and the maximum tolerated dose was not identified. The summary of adverse events by dose level is provided in the appendix (pp 6–7). Among the 22 patients included in the first nine dose levels, intra-patient dose escalation occurred in 19 (86%) patients and escalation to the maximal administered dose of 10 mg/kg occurred in 11 (44%) patients. Taking into account IPH4102 pharmacodynamic and pharmacokinetic profiles, the absence of dose-limiting toxicities, and that the maximum tolerated dose was not reached, the study safety committee recommended using the maximal administered dose for the cohort expansion, which corresponded to a flat dose of 750 mg.

Table 2 summarises grade 1–2 adverse events that occurred in at least 10% of patients and all adverse events of grade 3 or worse. The most common adverse events were peripheral oedema (12 [27%]) and fatigue (nine [20%]), which were all grade 1–2. Lymphopenia was the most frequent IPH4102-related adverse event and occurred in six (14%) patients (three [7%] grade 3). Infusion-related reactions was reported in three (7%) patients at different dose levels, two patients at the 750 mg dose level, and one at the 0·20 mg/kg dose level. Six grade 3–4 possibly treatment-related adverse events were reported in five patients: grade 4 sepsis (n=1), grade 3 aspartate aminotransferase increase (n=1), grade 3 lymphopenia (n=3), and grade 3 hypotension (n=1). No immune-mediated reactions related to IPH4102 were reported. Four patients permanently discontinued IPH4102 because of an adverse event: grade 2 peripheral neuropathy (n=one, 750 mg), grade 3 malaise (n=one, 6 mg/kg), grade 3 skin pain (n=one, 750 mg), and grade 4 sepsis (n=one, 750 mg).

Two patients had liver toxicity grade 3 or worse, including one patient who developed fulminant hepatitis 6 weeks after discontinuing IPH4102 that led to death. The latter was a 75-year-old patient who received four lines of cytotoxic chemotherapy among other systemic therapies before starting IPH4102 and had several associated comorbidities. He had a partial response to IPH4102, lasting for 1 year before developing disease progression. He had normal liver function and lymphocytic count throughout the treatment course. Investigations revealed positive human herpes virus-6B (HHV-6B) serology, confirmed by PCR in serum and liver biopsy. The liver function parameters of all the remaining patients were otherwise uneventful (appendix p 8) except for one patient who developed isolated grade 3 elevated aspartate aminotransferase while on treatment, which recovered to baseline 2 weeks later.

	Dose escalation (n=25)	Cohort expansion (n=19)	Patients with Sézary syndrome (n=35)*
Age, years	71 (62–79)	64 (54–71)	70 (62–78)
Sex			
Female	13 (52%)	5 (26%)	17 (49%)
Male	12 (48%)	14 (74%)	18 (51%)
ECOG performance status			
0	16 (64%)	12 (63%)	21 (60%)
1	8 (32%)	6 (32%)	12 (34%)
2	1 (4%)	1 (5%)	2 (6%)
CTCL subtype			
Mycosis fungoides	4 (16%)	4 (21%)	NA
Sézary syndrome	20 (79%)	15 (79%)	35 (100%)
CD4+ T-cell lymphoma, not otherwise specified	1 (5%)	0	NA
Evidence of large-cell transformation according to central assessment	7 (28%)	5 (26%)	6 (17%)
Clinical stage at study entry (mycosis fungoides or Sézary syndrome)			
IB	1 (4%)	1 (5%)	1 (3%)†
IIB	3 (12%)	3 (16%)	0
IIA	0	1 (5%)	0
IVA1	20 (80%)	11 (58%)	31 (89%)
IVA2	0	2 (11%)	2 (6%)
IVB	0	1 (5%)	1 (3%)
IPH4102 dose			
10 mg/kg or 750 mg as starting dose	3 (12%)	19 (100%)	16 (46%)
10 mg/kg or 750 mg as highest dose	11 (44%)	19 (100%)	24 (69%)
Time from initial CTCL diagnosis to starting IPH4102, months	46 (19–77)	22 (12–69)	23 (13–59)
KIR3DL2-expressing cells ≥ 5%			
Skin	22 (88%)	10 (53%)	27 (77%)
Blood	20 (80%)	12 (63%)	32 (91%)
Skin, blood, or both	25 (100%)	13 (68%)	33 (94%)
Number of prior systemic therapies received	4 (2–6)	2 (2–4)‡	2 (2–4)
Previous treatment received			
Bexarotene	20 (80%)	11 (58%)	24 (69%)
Methotrexate	17 (68%)	8 (42%)	19 (54%)
Interferon alpha	12 (48%)	9 (47%)	16 (46%)
Extracorporeal photopheresis	11 (44%)	6 (32%)	17 (49%)
HDAC inhibitors§	9 (36%)	9 (47%)	13 (37%)
Mogamulizumab	7 (28%)	2 (11%)	7 (20%)
Gemcitabine	6 (24%)	4 (21%)	7 (20%)
Brentuximab vedotin	3 (12%)	1 (5%)	2 (6%)

Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group. CTCL=cutaneous T-cell lymphoma. NA=not applicable. HDAC=histone deacetylase. *Patients included from both the dose-escalation and cohort-expansion parts. †One patient had history of having stage IVB Sézary syndrome but had low blood involvement at study entry (stage B1). As per protocol, the patient was deemed to have Sézary syndrome. ‡One patient had a protocol violation and received only one line of previous systemic therapy. §Romidepsin, vorinostat, or both.

Table 1: **Patient characteristics**

	All adverse events			Possibly treatment-related adverse events*		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Peripheral oedema	12 (27%)	0	0	1 (2%)	0	0
Asthenia	9 (20%)	0	0	5 (11%)	0	0
Fatigue	9 (20%)	0	0	3 (7%)	0	0
Cough	7 (16%)	0	0	0	0	0
Pyrexia	7 (16%)	0	0	3 (7%)	0	0
Diarrhoea	7 (16%)	0	0	2 (5%)	0	0
Arthralgia	7 (16%)	0	0	2 (5%)	0	0
Lymphopenia	3 (7%)	3 (7%)	0	3 (7%)	3 (7%)	0
Fall	6 (14%)	0	0	0	0	0
Headache	6 (14%)	0	0	1 (2%)	0	0
Hypertension	3 (7%)	2 (5%)	0	0	0	0
Anaemia	4 (9%)	1 (2%)	0	1 (2%)	0	0
Constipation	5 (11%)	0	0	1 (2%)	0	0
Dyspnoea	5 (11%)	0	0	1 (2%)	0	0
Chills	5 (11%)	0	0	3 (7%)	0	0
Rash	3 (7%)	1 (2%)	0	1 (2%)	0	0
Confused state	1 (2%)	1 (2%)	1 (2%)	0	0	0
Malaise	2 (5%)	1 (2%)	0	0	0	0
Pain of skin	2 (5%)	1 (2%)	0	0	0	0
Staphylococcal sepsis	0	0	1 (2%)	0	0	0
Acute kidney injury	1 (2%)	0	1 (2%)	0	0	0
Tremor	1 (2%)	1 (2%)	0	1 (2%)	0	0
Dysphagia	1 (2%)	1 (2%)	0	0	0	0
Delirium	1 (2%)	1 (2%)	0	0	0	0
Acute respiratory failure	0	0	1 (2%)	0	0	0
Sepsis	0	0	1 (2%)	0	0	1 (2%)
Postoperative wound infection	0	1 (2%)	0	0	0	0
Squamous-cell lung cancer	0	1 (2%)	0	0	0	0
Hypoalbuminaemia	0	1 (2%)	0	0	0	0
Aspartate aminotransferase increase	0	1 (2%)	0	0	1 (2%)	0
Hip fracture	0	1 (2%)	0	0	0	0
Hallucination	0	1 (2%)	0	0	0	0
Hypotension	0	1 (2%)	0	0	1 (2%)	0

*Possibly treatment-related adverse event as defined by the treating investigator.

Table 2: **Summary of adverse events grade 1–2 occurring in at least 10% of patients and all grade 3 or worse adverse events**

At the data cutoff date of Oct 15, 2018, median follow-up for the whole population was 14·1 months (IQR 11·3–20·5) and seven patients were still ongoing treatment. All patients had at least one post-baseline assessment. In the activity population (n=44), confirmed global overall response was achieved in 16 (36·4% [95% CI 23·8–51·1]) patients, median duration of response was 13·8 months (IQR 7·2–not reached), and median progression-free survival after 29 progression-free survival events was 8·2 months (95% CI 7·1–17·2).

In the subset of patients who had Sézary syndrome (n=35), 15 (43% [95% CI 28·0–59·1]) patients achieved a confirmed global overall response (figure 2A). Response by compartment is detailed in the appendix (p 9). The median duration of response was 13·8 months (95% CI 7·2–not reached; figure 2B) and median progression-free survival after 21 progression-free survival events was 11·7 months (8·1–not reached; figure 2C). Clinical activity according to the initially administered dose-level is provided in the appendix (p 15). No responses were observed in the six patients with Sézary syndrome who had evidence of large-cell transformation at baseline. In a post-hoc analysis of seven patients with Sézary syndrome who were previously treated with mogamulizumab, three (43%) achieved a global overall response and three others had stable disease as best response. The remaining patient had progressive disease. The median duration of response in these patients was 13·8 months (IQR 7·2–not reached) and median progression-free survival after five progression-free survival events was 16·8 months (95% CI 8·1–not reached).

Nine (20%) patients were diagnosed with other cutaneous T-cell lymphoma subtypes that were not Sézary syndrome. Eight patients had mycosis fungoides, of whom five had evidence of large-cell transformation. One patient with mycosis fungoides achieved a confirmed global response that lasted for 6·9 months. The remaining patients had stable disease as their best global response. The median progression-free survival (eight progression-free survival events) was 3·9 months (95% CI 3·0–not reached). One patient had CD4+ primary cutaneous peripheral T-cell lymphoma, not otherwise specified. This patient had stable disease as a best global response and progressed on week 18.

Compliance with quality-of-life questionnaires was high; 468 (97%) of 484 of the VAS and 459 (95%) of 484 of the Skindex-29 questionnaires were completed. Treatment with IPH4102 was associated with a decrease in pruritus by VAS (figure 3A) and a decrease in Skindex-29 global scores (figure 3B), as well as symptoms, emotions, and functioning scores (figure 3C, 3D, 3E), over time.

IPH4102 serum levels remained below the lower limit of quantification (100 ng/mL) at the 0·0001 mg/kg and 0·001 mg/kg dose levels. The pharmacokinetic profile of IPH4102 was linear and dose-proportional from 0·75 mg/kg to 6 mg/kg, with slight accumulation occurring at 10 mg/kg during the weekly schedule (appendix p 10). In the dose-escalation part, IPH4102 concentration exhibited a classical two-phase exponential decrease following each infusion as of the 0·05 mg/kg dose-level (appendix p 16). In the cohort-expansion part, IPH4102 serum concentration remained greater than 20 µg/mL in all patients, irrespective of the frequency of dosing (appendix p 16).

Four (9%) of 44 patients were positive for anti-drug antibodies, one in the dose-escalation and three in the cohort-expansion, of which only one was considered

treatment-related. This patient developed anti-drug antibodies in week 10 and subsequently developed several episodes of grade 2 infusion-related reaction resulting in treatment discontinuation at week 36. In the three other patients, one tested positive before starting therapy and the two others were positive at a single timepoint only. None of these patients showed any substantial change in IPH4102 pharmacokinetics profile and none developed infusion-related reactions, hence they were deemed to be unrelated to IPH4102 exposure.

At baseline, aberrant Sézary cells in the blood ranged from 459 to 17 410 cells per µL (median 2984 cells per µL) in the dose-escalation part and from 150 to 10 301 cells per µL (median 1234 cells per µL) in the cohort-expansion part. The specific clonotypic surface T-cell receptor (Vbeta chain) was assessed for all patients with Sézary syndrome at baseline and was identified in 19 (54%) of 35 patients, and subsequently monitored by flow cytometry throughout treatment. The median percentage of clonotypic cells expressing KIR3DL2 was 89% (range 26–100) in the dose-escalation part and 57% (0–99) in the cohort-expansion part. Available clonotypic information is provided in the appendix (pp 11–12).

In the blood, IPH4102 did not reduce the count of KIR3DL2-expressing natural-killer cells (data not shown). Descriptive analysis showed that treatment with IPH4102 resulted in an early reduction in the concentration of aberrant Sézary cells and circulating KIR3DL2-expressing CD4+ T-cells (figure 4A, 4B).

In a post-hoc analysis, no clear correlation was observed between the degree of KIR3DL2 expression in the skin at baseline and response to IPH4102 (data not shown). Biopsies before and after treatment were obtained in 31 (89%) of 35 patients with Sézary syndrome. At least a 50% reduction of KIR3DL2-expressing cells in skin or minimal residual disease in blood at week 5 was associated with a higher proportion of patients achieving a global overall response, a longer duration of response, and longer progression-free survival (appendix p 13). Similar results were observed on week 14 for minimal residual disease and KIR3DL2 expression in both skin and blood compartments (appendix p 14).

Discussion

This study investigated the safety and activity of IPH4102 in patients with relapsed or refractory cutaneous T-cell lymphoma. IPH4102 showed a favourable safety profile and was associated with high frequency of durable global response and an improvement of quality of life, particularly in the subset of patients who had Sézary syndrome, which represented most patients included in this trial.

No dose-limiting toxicities or IPH4102 immune-related adverse events were observed and only four patients stopped treatment due to an adverse event. This result compares favourably with the safety profile of available systemic therapies for patients with cutaneous T-cell lymphoma. One patient developed hepatitis that was

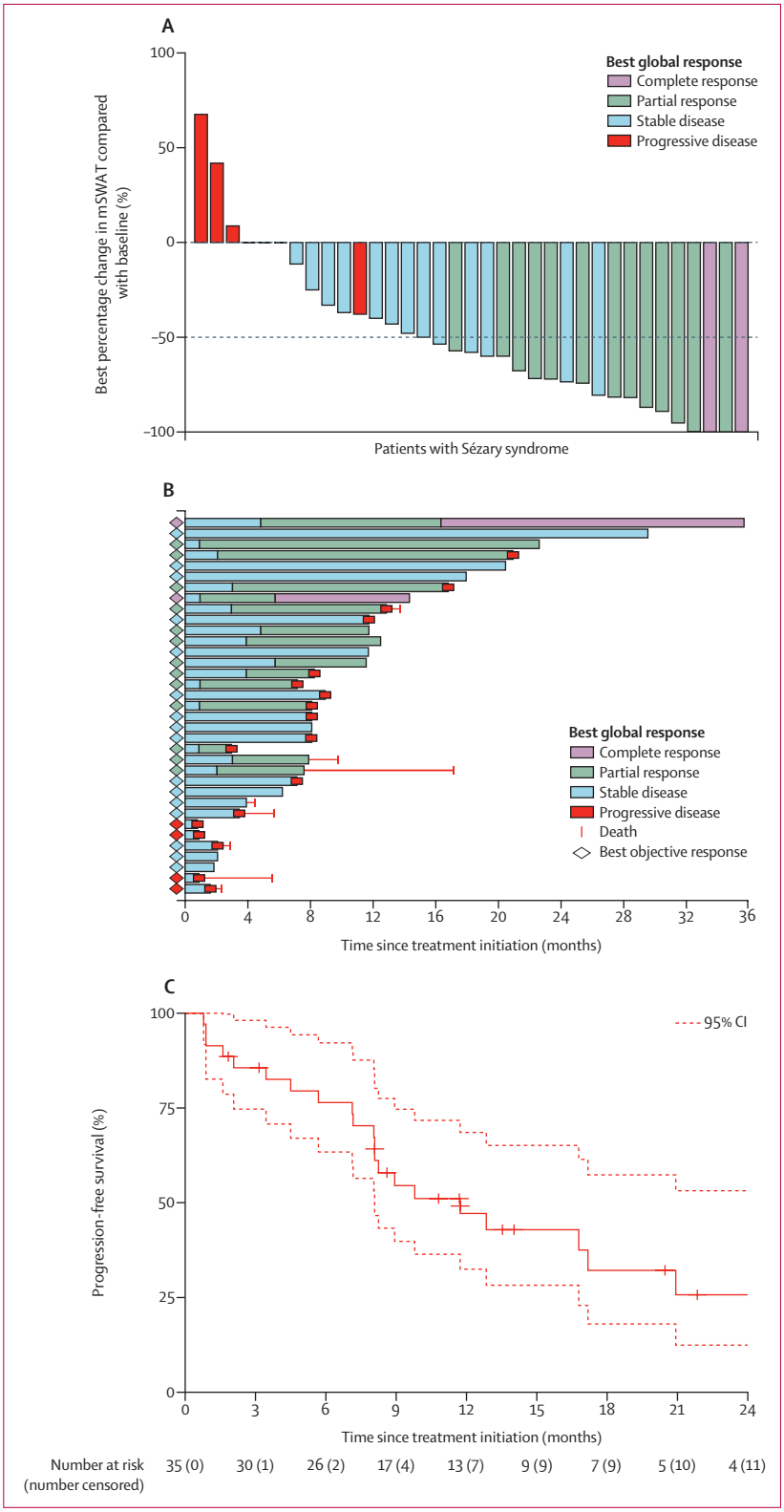

Figure 2: **Clinical activity of IPH4102 in patients with Sézary syndrome (n=35)**
(A) Waterfall plot showing the best change in mSWAT from baseline. (B) Swimmer plot showing individual patients and their duration of response. (C) Kaplan-Meier estimate of progression-free survival with 95% CIs. mSWAT=modified severity weighted assessment tool.

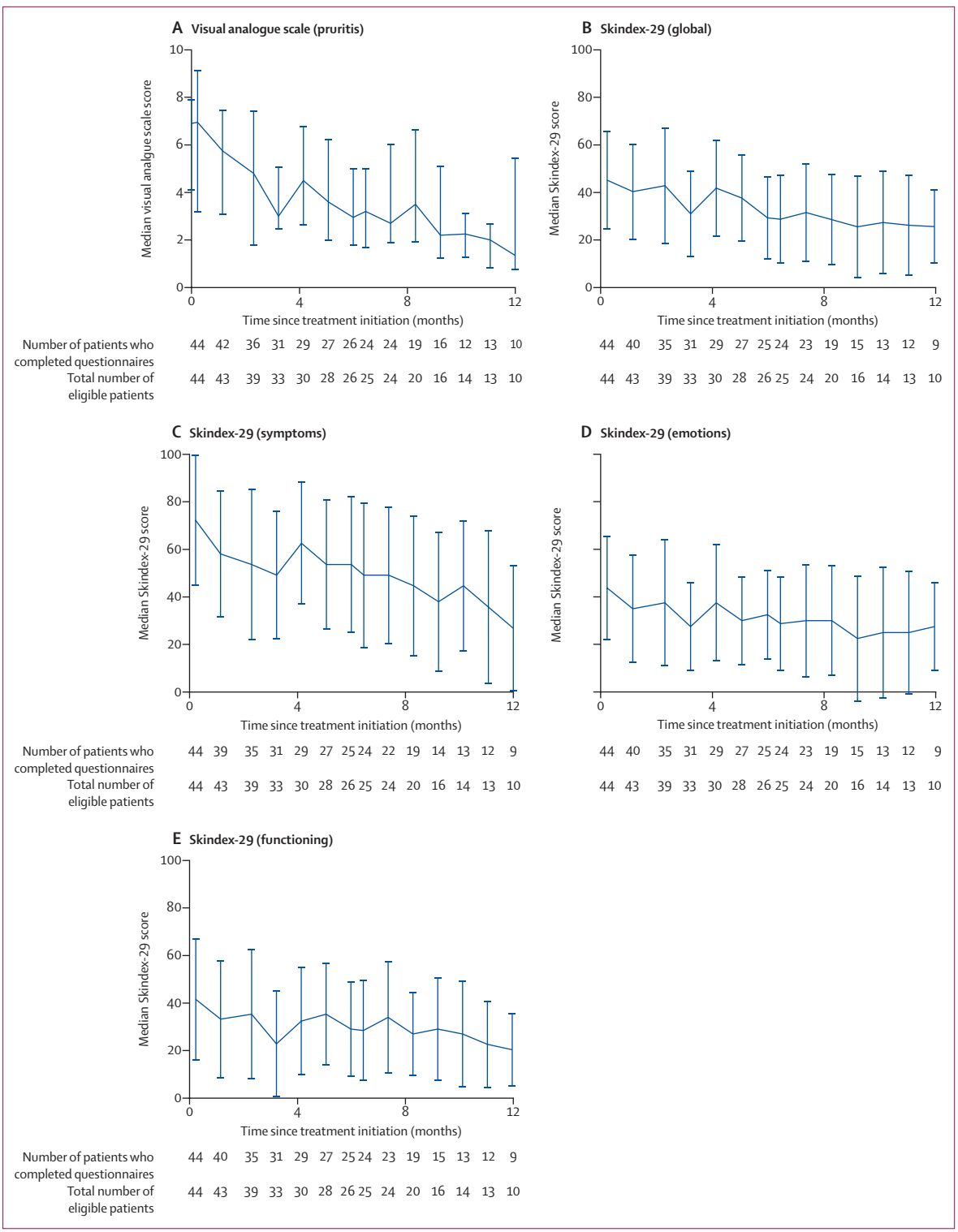

Figure 3: **Effect of IPH4102 on quality of life in all patients during the first year of treatment (n=44)**
The error bars represent SDs.

possibly IPH4102-related 6 weeks after treatment discontinuation, which subsequently led to death. However, this patient had a positive viral load of HHV-6B in both serum and liver tissue, which has been previously shown to result in death, particularly in immunocompromised patients.[18,19] Acknowledging the limited changes in on-

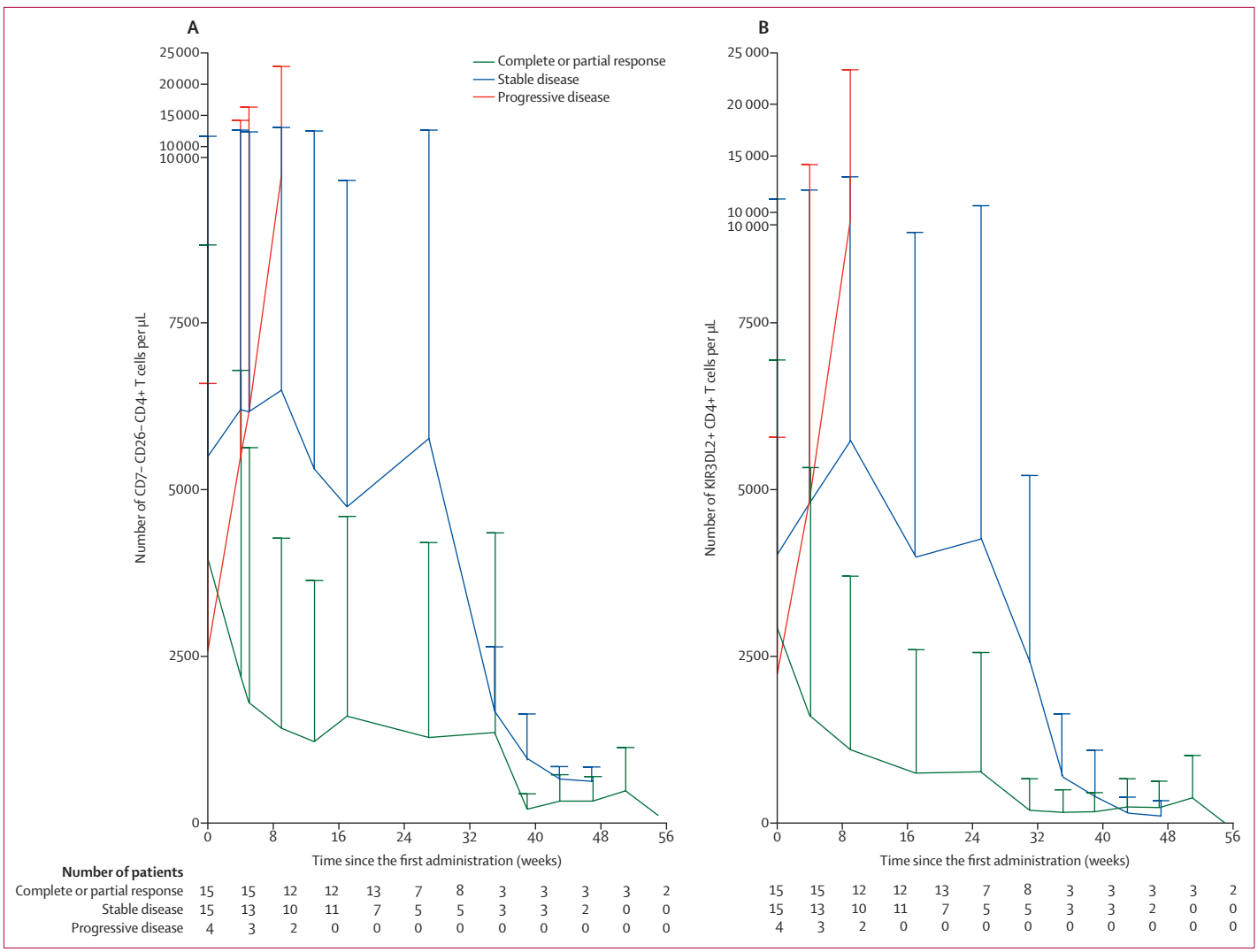

Figure 4: **Immunomonitoring of blood cells during treatment with IPH4102**
(A) Mean count of aberrant Sézary cells (CD7– CD26–CD4+) per µL blood, throughout treatment, identified by multicolour flow cytometry. (B) Mean count of KIR3DL2+ CD4+ T cells per µL blood, throughout treatment, identified by multicolour flow cytometry. The error bars represent SDs.

treatment liver functions reported in this study and considering the profile of the included patients (elderly and heavily pre-treated), we believe that the observed hepatic safety profile of IPH4102 is reassuring.

Six patients (14%) developed lymphopenia, of which half were grade 3–4, yet none resulted in opportunistic infections. KIR3DL2 is expressed on around 30% of natural-killer cells;[20] however, we did not find that IPH4102 reduces the count of KIR3DL2-expressing natural-killer cells. The observed lymphopenia is possibly a result of IPH4102 reducing the CD4 neoplastic lymphocytosis, thus unmasking an underlying lymphopenia caused by the disease, a phenomenon that is common in cutaneous T-cell lymphoma.[21]

In patients with Sézary syndrome, IPH4102 showed a high global and blood response. Importantly, these responses were long-lived with median durations of response and progression-free survival of approximately 1 year. Only four out of 35 patients with Sézary syndrome had progressive disease as a best response, which indicates that more than 85% of patients derived benefit. In earlier treatment lines, extracorporeal photopheresis is widely used, with an overall response of around 43%.[22] More recently, mogamulizumab received regulatory approval in patients with mycosis fungoides or Sézary syndrome who received at least one prior systemic therapy, showing that 37% of patients achieved an overall response in the Sézary syndrome subgroup.[8] In our study, IPH4102 showed similar clinical activity, but with a favourable toxicity profile and in a more refractory patient population. Of note, vorinostat is the only FDA-approved drug in managing patients with cutaneous T-cell lymphoma who have received at least two prior systemic therapies, a population similar to the one treated in our trial.[15] In a phase 3 trial,

the drug showed an overall response of only 2% in patients with Sézary syndrome.[8] Thus, the observed clinical activity with IPH4102, if confirmed in subsequent trials, would represent a paradigm shift in managing patients with relapsed or refractory Sézary syndrome.

Responses seemed to be restricted to patients without large-cell transformation. These results need to be interpreted with caution because only six patients with Sézary syndrome had evidence of large-cell transformation at baseline. Large-cell transformation is a histological feature observed in 10–20% of patients at diagnosis and has been shown to be associated with poor outcomes.[23] Of note, patients with large-cell transformation were excluded from the trial that led to the approval of mogamulizumab in patients with mycosis fungoides or Sézary syndrome who received at least one prior systemic therapy.[8] A post-hoc analysis showed that IPH4102 had clinical activity in patients who were previously treated with mogamulizumab, similar to that observed in the whole population, suggesting that previous treatment with mogamulizumab might not affect responses to IPH4102. Further confirmation of IPH4102 activity in patients previously treated with mogamulizumab in future studies is underway.

Quality of life represents a major concern for patients with cutaneous T-cell lymphoma, particulary Sézary syndrome, in which nearly 90% of patients have severe debilitating pruritus,[4] with a profound effect on employment, relationships, and social wellbeing.[24] In our trial, most patients showed notable improvement in various quality-of-life parameters, including itching.

Only eight patients with mycosis fungoides were treated in this study, of whom four (50%) had no evidence of KIR3DL2 expression. Thus, the potential magnitude of benefit of IPH4102 in these patients is hard to reliably estimate. Studies are underway to better characterise the activity of IPH4102 and the value of KIR3DL2 testing in patients with mycosis fungoides.

This study has some limitations that should be taken into account. Although the observed clinical activity of IPH4102 and its effect on quality of life in patients with Sézary syndrome is promising, this study was not powered to provide definite conclusions on these fronts and thus these findings require further confirmation. Additionally, we could not draw conclusions about the dose–response relationship because intra-patient dose-escalation took place in most patients in the dose-escalation part of the study.

In conclusion, this study provides preliminary encouraging evidence showing that IPH4102 could emerge as a promising treatment option in patients with relapsed or refractory Sézary syndrome. On the basis of these results, the FDA has granted (on Jan 17, 2019), fast-track designation for IPH4102 in managing these patients. A phase 2 study (TELLOMAK, NCT03902184) is underway to confirm the clinical activity in Sézary syndrome and investigate the potential of IPH4102 in other T-cell lymphomas that express KIR3DL2.

Contributors

MB, PP, BMW, MV, SW, HAA Jr, and YHK formed the safety committee of the study, designed the trial, collected and analysed data, drafted the report, revised it critically, and gave final approval to submit for publication. AM-C, MB, CR-W, MSK, and AB, collected data, drafted the report, revised it critically, and gave final approval to submit for publication. FR, CP, CB, HS, and HAA Jr analysed data, drafted the report, revised it critically, and gave final approval to submit for publication.

Declaration of interests

MB reports personal fees from Kyowa Kirin and Innate Pharma; investigator fees from Innate Pharma, Takeda, Kyowa Kirin, and Galderma; speaker bureau fees from Actelion; consultant fees from Innate Pharma, Takeda, Kyowa Kirin, and miRagen; and a patency (IPH4102). PP reports personal fees from and working as a scientific advisor for Innate Pharma, and providing research support for Kyowa Kirin and Viracta. MB reports working as a consultant for Innate Pharma, Bristol-Myers Squibb, and Leo-Pharma; and a grant from Takeda. BMW reports a grant from Innate Pharma, providing clinical trial support for Celgene, and working on an advisory board for miRagen. CR-W reports working as an investigator for Innate Pharma, Kyowa Kirin, and Takeda. AB reports a patent (IPH4102).YHK reports personal fees and grants from Kyowa Kirin; grants from Merck, Soligenix, Forty-Seven, Neumedicines, Portola Pharma, and Horizon; and personal fees from Eisai, Takeda, Seattle Genetics, miRagen, and Innate Pharma. FR, CP, CB, HS, and HAA Jr report employment and possible stock options in Innate Pharma. All other authors declare no competing interests.

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