IPH4102, a first-in-class anti-KIR3DL2 monoclonal antibody in patients with refractory cutaneous T cell lymphoma: An international multicentre phase 1 trial.

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Summary

Background: IPH4102 is a first-in-class monoclonal antibody targeting KIR3DL2, a cell surface protein expressed in cutaneous T cell lymphoma (CTCL), mainly its leukemic form, Sézary Syndrome (SS). In this study, we evaluated the safety and activity of IPH4102 in CTCL.

Methods: This is a first-in-human, phase 1 clinical trial with dose-escalation and cohort-expansion portions. Eligible patients had relapsed/refractory CTCL, PS ≤2, age ≥18years and should have received ≥two systemic therapies. Ten dose-levels of IPH4102, administered as an intravenous infusion, ranging from 0·0001-10mg/kg were evaluated using an accelerated 3+3 design. Primary objective was safety. Secondary and exploratory objectives included clinical activity, quality of life (QOL), and biomarker analyses. Safety and efficacy analyses were done per-protocol. The study is ongoing and recruitment is complete (clinicaltrials.gov: NCT02593045).

Findings: From November 2015 – November 2017, 44 patients were enrolled (median age: 69years). 35 patients (80%) had SS, 8 (18%) had mycosis fungoides and 1 (2%) had primary cutaneous T-cell lymphoma, not-otherwise specified. Median prior systemic therapies was 3. In the dose-escalation, no dose-limiting toxicity was identified and the trial's safety committee recommended a flat dose of 750mg for the cohort-expansion, corresponding to the maximum administered dose. Most common adverse events (AEs) were peripheral oedema (27%), and fatigue (20%). Lymphopenia was the most common grade 3-4 AE (7%). One patient developed fulminant hepatitis following IPH4102 discontinuation and subsequently died with evidence of HHV-6B infection. In the efficacy population (n=44, 100%), median follow-up was 14·1months (IQR: 11.3-20.5). Confirmed global overall response rate (ORR), duration of response (DOR) and progression-free survival (PFS) were 36·4% [95% CI: 23·8% – 51·1%], 13·8 [95% CI: 7·2% – NR] and 8·2 months [95% CI: 7·1% – 17.2], respectively. . In the SS subset (n=35, 80%),

confirmed global ORR, median DOR and PFS were 42·9% [95% CI: 28·0% – 59·1%], 13·8 [95% CI: 7·2 – NR] and 11·7 [95% CI: 8·1 – NR] months, respectively. Confirmed ORR in skin, blood and lymph node compartments were 51.4%, 55.9% and 11.1%, respectively, with 26.5% of patients experiencing complete response in the blood. Marked improvement in QOL and pruritus scores was observed. To date, 7 SS patients (20%) are still receiving IPH4102.

Interpretation: IPH4102 is safe and shows encouraging clinical activity in relapsed/refractory SS. If confirmed, IPH4102 would emerge as a novel treatment option for these patients. Further studies are underway.

Funding: Innate Pharma

Research in context

Evidence before this study

Cutaneous T-cell Lymphoma (CTCL) is an uncommon and incurable form of non-Hodgkin lymphoma. Sézary Syndrome (SS) represents around 5-10% of CTCL, and is considered its leukemic and most aggressive form with median survival hardly exceeding 4 years. These patients typically suffer devastating pruritus, frequent infections, and body disfigurement resulting in very poor quality of life. In 2018, two novel agents; brentuximab vedotin and mogamulizumab were approved for the treatment of subsets of patients with CTCL who received at least one prior systemic therapy. However, only mogamulizumab included SS patients in its pivotal trial. In more refractory patients (i.e. who received at least two prior systemic therapies), no agents are proven to be effective particularly in SS. Vorinostat is the only approved agent in the US showing in a recent trial an overall response rate of 2.3% in Sézary Syndrome and progression free survival in the range of 3 months.

KIR3DL2 (CD158k) is a member of the highly polymorphic family of killer-cell immunoglobulin like receptors (KIRs). It is widely expressed in CTCL, particularly SS in more than 85% of patients and was recently proposed as the most sensitive diagnostic and prognostic marker for SS patients.

We searched the scientific literature to identify reports of patients with CTCL, SS and KIR3DL2. We searched MEDLINE for studies published in English until December 31, 2018. Search items included “Cutaneous T-cell lymphoma”, “KIR3DL2”, and Sézary Syndrome”.

Added value of this study

This is the first reported trial of the anti-KIR3DL2; IPH4102 in the literature. Unlike the very few previous studies focused on patients with refractory CTCL who received at least two prior

systemic therapies, this study uses the current international consensus response criteria incorporating skin, blood, lymph node and visceral responses. This study shows impressive activity of IPH4102 in SS patients who received at least two prior systemic therapies, as shown by a confirmed global response of 42·9%, duration of response of 13·8 months and progression free survival of 11·7 months. The treatment was very well tolerated with no identified dose-limiting toxicity in the dose escalation portion of the study. IPH4102 also resulted in the improvement of the quality of life of the majority of patients treated. These results represent a new paradigm shift in managing patients with refractory SS.

Implications of all available evidence

The study reports an exceptional activity of a novel targeted agent in a rare form of CTCL; SS with very high unmet medical need. These results led to the US Food and Drug Administration designating a Fast Track development program the investigation of IPH4102 for the treatment of adult patients with relapsed or refractory SS who have received at least two prior systemic therapies. A pivotal trial in SS is currently underway along with a phase 2 program investigating the role of IPH4102 in other T-cell malignancies that express KIR3DL2.

Introduction

Cutaneous T-cell lymphomas (CTCL) are a heterogeneous group of rare extra-nodal non-Hodgkin lymphomas, with approximately 3,000 new cases diagnosed in the US every year[1]. The most common subtype of CTCL is mycosis fungoides (MF) that accounts for 50 – 60% of all cases[2]. Sézary syndrome (SS) is a rare leukemic subtype characterized by erythroderma, lymphadenopathy and high burden of neoplastic T-cells (Sézary cells) in the blood[3]. SS patients typically suffer devastating pruritus, frequent infections, and body disfigurement resulting in very poor quality of life (QOL)[4]. Prognosis is dismal with median survival ranging from 2.5 – 4 years[5, 6].

Recently, based on the results of two randomized trials, brentuximab vedotin and mogamulizumab were approved for the treatment of subsets of patients with CTCL who received at least one prior systemic therapy[7, 8]. Only mogamulizumab included SS patients in its pivotal trial. In more refractory patients (i.e. who received at least two prior systemic therapies), vorinostat is the only approved agent in the US with modest clinical activity in SS[8].

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

IPH4102 is a humanized first-in-class monoclonal antibody designed to deplete KIR3DL2-expressing cells via antibody-dependent cell-cytotoxicity and phagocytosis[11]. It has shown anti-tumour activity in mouse xenograft models and *ex-vivo* autologous assays using patient-derived natural killer (NK) and Sézary cells[11]. Here we report the results of the first-in-human phase 1 study evaluating IPH4102 in patients with relapsed/refractory CTCL.

Methods

Study design and participants

This was an international, open-label, phase 1, multicentre study evaluating IPH4102 in patients with relapsed/refractory CTCL. The study was composed of dose-escalation and cohort-expansion portions. It was conducted in five academic hospitals in the US, France, UK, and the Netherlands in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines. The study was designed by the Sponsor; Innate Pharma together with the study investigators. The study protocol was approved by the institutional review board at each participating site. All patients signed informed consent before being screened.

Eligible patients had relapsed/refractory histologically confirmed primary CTCL, aged ≥ 18 years, received at least two prior systemic therapies, and had an Eastern Cooperative Oncology group performance score ≤ 2.In the dose-escalation part, and based on a scientific advice from the European Medical Agency in November 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 CTCL subtypes known to express KIR3DL2 in the majority of patients[9]; SS and MF with evidence of large cell transformation (LCT) with target recruitment of 15 patients in each cohort. A protocol amendment was performed in March 2017 to allow recruitment of patients irrespective of KIR3DL2 expression in the cohort-expansion. Further details regarding inclusion and exclusion criteria are provided in the Appendix (page 3).

A safety data-monitoring committee constituted of study investigators and representatives from the sponsor convened at regular intervals to overview the safety of trial subjects, and particularly inform on dose-escalation decisions, declaration of dose limiting toxicities (DLTs), the maximum tolerated dose (MTD) and the recommended phase 2 dose.

Procedures

The first tested dose was 0·0001 mg/kg and intra-patient dose escalation was allowed. In the cohort-expansion, all patients were treated with the recommended dose based on the results of the dose-escalation part. Treatment was administered as one-hour infusion weekly for the first month, every two weeks x 10 administrations, and then every 4 weeks until disease progression or unacceptable toxicity. No dose reductions were allowed. Dose interruption due to an adverse event (AE) was allowed up to a maximum of 4 weeks. The protocol recommended permanent discontinuation of IPH4102 in case of severe infusion related reaction (IRR), unresolved grade 3 liver toxicity, or other AEs requiring discontinuation according to the investigator's assessment. AEs were graded according to the National Cancer Institute Common Terminology Criteria for AEs, version 4.0[12]. Overall response was evaluated using the global composite response score based on response in each compartment, as described in the international consensus criteria (Appendix, page 6)[13]; with skin response evaluated using the modified Severity Weighted Assessment Tool (mSWAT)[14]. In the dose-escalation, either flow cytometry or cytomorphology was used to evaluate blood response based on investigator's preference. In the cohort-expansion, only flow cytometry was used. Skin and blood compartments were evaluated every 4 weeks throughout the study. Lymph node and visceral involvement were evaluated at baseline using MRI, CT or PET scan at the discretion of the investigator. If positive, follow-up imaging was performed at week 5 and then every 12 weeks thereafter. QOL was evaluated with each IPH4102 infusion using Skindex-29[15] and pruritus visual analogue score (VAS)[16].

KIR3DL2 was evaluated by immunohistochemistry (IHC) using an anti-KIR3DL2 antibody (clone 12B11, mouse IgG1 isotype). Another antibody was used for assessment by flow cytometry (clone 13E4, mouse IgG1 isotype). Both antibodies bind to KIR3DL2 on different epitopes than IPH4102. Detection of antidrug antibodies (ADA) was based on

electrochemoluminescence via a bridging format that uses a mix of biotin-labelled IPH4102 and SULFO-TAG-labelled IPH4102.

KIR3DL2 expression and histological evaluation of LCT were performed centrally at Saint Louis Hospital (Paris, France). Pharmacokinetics (PK)/immunogenicity, IHC and minimal residual disease (MRD) were performed by Quality Assistance (Donstiennes, Belgium), Histalim (Montpellier, France), and Adaptive Biotechnologies (Seattle, Washington, US), respectively, under the paid supervision of the sponsor. Immunomonitoring was performed centrally at Saint Louis Hospital for European sites and in the US at ABL (Rockville, Maryland) during the dose-escalation and Caprion Biosciences (Montréal, Canada) during the cohort-expansion.

Outcomes

The primary endpoint was the occurrence of DLTs during the first two weeks of treatment, defined as: grade ≥3 toxicity lasting for ≥8 days, except lymphopenia; or grade ≥4 symptoms judged to be consistent with an IRR/ cytokine release syndrome without premedication; or grade ≥3 symptoms judged to be consistent with a recurrent IRR/cytokine release syndrome despite premedication; or grade ≥3 tumour lysis syndrome. Secondary endpoints are detailed in the Appendix (page 4) and included PK, immunogenicity and QOL endpoints in addition to several efficacy endpoints like overall response rate (ORR), duration of response (DOR) and progression free survival (PFS).

Exploratory objectives comprised the characterization of pharmacodynamics biomarkers in skin (by IHC) and blood (by flow cytometry), through monitoring of KIR3DL2-expressing cells before and during treatment. MRD was assessed using high throughput sequencing of the clonal TCR rearrangements of neoplastic T-cells in the skin and blood. Other exploratory biomarker analysis were evaluated but will be reported elsewhere and included evaluation of NK cell, macrophage infiltration, other immune receptors, cytokine release, and gene expression pattern.

Statistical Analysis

In the dose-escalation, an accelerated 3+3 design was adopted to determine the MTD[17]. One patient was treated at each of the first three dose levels, and subsequently three patients were treated per dose level until the maximal administered dose (MAD) of 10 mg/kg. Cohort expansion was designed to confirm the safety of the recommended dose and investigate clinical activity without a priori assumption regarding sample size.

Safety data were summarized for the safety population; patients who received at least one dose of IPH4102. Efficacy analysis was performed according to CTCL subtype (i.e. SS, MF) for the efficacy population; patients who received at least one dose of IPH4102, and had a baseline disease assessment and at least one subsequent scheduled disease assessment. Response was assessed between the first administered dose until end of treatment. In order 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[13].

DOR and PFS were estimated using the Kaplan–Meier method and were censored at the latest disease assessment. QOL analysis is detailed in the Appendix (page 5). The association between exploratory biomarkers, evaluated on weeks five and 14, and clinical activity was evaluated using descriptive statistics. All statistical analyses were performed using SAS 9.3 and R 3.5.

The 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 performed by the Sponsor. All authors including representatives from the Sponsor contributed to the development 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 decision to submit for publication.

Results

From November 4, 2015 through November 20, 2017, a total of 54 patients with relapsed/refractory CTCL were screened of whom 44 patients were enrolled and received at least one dose of IPH4102 (Figure 1). Twenty-five patients were included in the dose-escalation. In the cohort-expansion, recruitment was restricted to 15 SS and four MF with LCT due to shortage in drug supply.

Main patient characteristics are summarized in table 1. Median age was 69 years (interquartile range: 58 – 76) and nearly 80% (n=35) of patients had SS and stage IV disease. As per protocol, all patients received at least two prior systemic therapies except for one patient, which was documented as a protocol violation. Seventeen patients (39%) received IPH4102 as the 5^{th} line of systemic therapy or more.

Flow cytometry assessment of SS patients showed that 27 (77%) had the CD3+CD4+CD26- phenotype while 7 (20%) had the CD3+CD4+CD7- phenotype. One patient displayed a CD26+CD7+ phenotype of his Sézary cells, thus they were alternatively identified and followed-up using the individual clonotypic surface TCR (Vbeta 2).

Ten dose-levels of IPH4102 were investigated, ranging from 0·0001 to 10 mg/kg. No DLTs were observed and the MTD was not identified. Summary of AEs per dose level are provided in the Appendix (page 7). Among the 22 patients included in the first 9 dose-levels, intra-patient dose escalation and escalation to the MAD of 10 mg/kg occurred in 86% (n=19) and 44% (n=11) of patients, respectively. Taking into account IPH4102 PD and PK profiles, the absence of DLTs

and that the MTD was not reached, the study safety committee recommended using the MAD for the cohort expansion, which corresponded to a flat dose of 750 mg.

Table 2 summarizes AEs that occurred in at least 10% of patients and all grade ≥ 3 AEs. Most common AEs were peripheral oedema (n=12, 27%), and fatigue (n=9, 20%), which were all grade 1-2. Lymphopenia was the most frequent IPH4102-related AE and occurred in six patients (14%). IRR were observed in three patients (7%) at different dose levels. Six grade 3-4 possibly-related AEs were reported in five patients: grade 4 sepsis (n=1), grade 3 transaminase increase (n=1), grade 3 lymphopenia (n=3), and grade 3 hypotension (n=1). No immune-mediated reactions related to IPH4102 were reported. In total, only 4 patients permanently stopped IPH4102 for an AE.

A total of two patients experienced ≥ grade 3 liver toxicity including one patient who developed fulminant hepatitis six weeks after discontinuing IPH4102 that lead to death. This 75 year-old patient received 4 lines of cytotoxic chemotherapy among other systemic therapies prior to starting IPH4102, and had several associated comorbidities. He had had partial response to IPH4102, lasting for one 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 both serum and liver biopsy. The second patient experienced isolated grade 3 AST increase while on treatment, which recovered two weeks later. Liver function parameters of all the remaining patients were otherwise uneventful (Appendix, page 9).

At the data cut-off date of October 15, 2018, median follow-up for the whole population was 14·1 months (interquartile range: 11·3 – 20·5) and seven patients were still ongoing treatment. All patients had at least one post-baseline assessment. In the efficacy population (n=44),

confirmed global ORR, DOR and PFS were 36·4% [95% CI: 23·8% – 51·1%], 13·8 months [95% CI: 7·2% – NR] and 8·2 months [95% CI: 7·1% –17.2], respectively.

In the SS subset (n=35, 80%), IPH4102 showed a confirmed global ORR of 42·9% [95% CI: 28·0% – 59·1%] (Figure 2A). Response by compartment is detailed in the Appendix (page 10). Median DOR (Figure 2B) and PFS were 13·8 months [95% CI: 7·2 – NR] and 11·7 months [95% CI: 8·1 – NR] (Figure 2C, 21 events), respectively. Clinical activity according to the initially administered dose-level is provided in the Appendix (page 16). Post-hoc analysis according to the presence of LCT at baseline and prior treatment with mogamulizumab was performed. No responses were observed in the 6 SS patients who had evidence of LCT at baseline. Seven SS patients were previously treated with mogamulizumab of whom three showed global OR (42·9%) and only one showed progressive disease as best response. Median DOR and PFS were 13· 8 [95% CI: 7·2 – NR] and 16·8 [95% CI: 8·1 – NR] months, respectively.

Only nine patients (20%) were diagnosed with other CTCL subtypes, of whom eight had MF and five had evidence of LCT. One patient developed confirmed global response that lasted for 6·9 months. The remaining MF patients had stable disease as best global response. Median PFS (8 events) was 3·9 months [95% CI: 3·0 – NR]. One patient had CD4+ primary cutaneous peripheral T-cell lymphoma, not-otherwise-specified. He experienced stable disease as best global response and progressed on week 18.

Compliance to QOL questionnaires was high; 97% and 95% of the VAS and Skindex questionnaires were completed, respectively. Treatment with IPH4102 was associated with a decrease in pruritus (Figure 3A) and Skindex global (Figure 3B) as well as symptoms, emotional and functional scores (Figure 3C-E) overtime.

IPH4102 serum levels remained below the lower limit of quantification (100 ng/mL) at the 0·0001 and 0·001 mg/kg dose levels. The PK profile of IPH4102 was linear and dose-

proportional from 0·75 to 6 mg/kg, with slight accumulation occurring at 10 mg/kg during the weekly schedule (Appendix, page 11). In the dose-escalation, IPH4102 concentration exhibited a classical two-phase exponential decrease following each infusion as of the 0·05 mg/kg dose-level (Appendix, page 17). In the cohort-expansion, IPH4102 serum concentration remained >20 µg/mL in all patients, irrespective of the frequency of dosing. Further details are provided in the Appendix (page 17).

Four patients (9%) were positive for ADA, one in the dose-escalation and three in the cohort-expansion, of whom only one was considered treatment-related. This patient developed ADA on week 10 and subsequently developed several episodes of grade 2 IRR resulting in treatment discontinuation on week 36. In the three other patients: one was tested positive before starting therapy while the two others were positive at a single time point only. None of these patients exhibited any significant change in IPH4102 PK profile and none developed IRR, hence they were considered un-related to IPH4102 exposure.

At baseline, aberrant Sézary cells ranged from 459 to 17,410 cells/µL (median: 2,984 cells/µL) in the dose-escalation and from 150 to 10,301 cells/µL (median: 1,234 cells/µL) in the cohort-expansion. The specific Vbeta was assessed for all SS patients at baseline. It was identified in 19 patients (54%), and subsequently monitored by flow cytometry throughout treatment. The median percentage of clonotypic cells expressing KIR3DL2 was 89% and 57% in the dose-escalation and cohort-expansion, respectively. Available clonotypic information is provided in the Appendix (page 12)

In blood, descriptive analysis showed that treatment with IPH4102 resulted in early reduction in the level of aberrant Sézary cells and circulating KIR3DL2 expressing CD4+ T-cells (Figure 4A-B).

In skin, no clear correlation was observed between the degree of KIR3DL2 expression at baseline and response to IPH4102 (data not shown). Pre-and post-treatment biopsies were obtained in 31 out of 35 patients (88.5%). A post-hoc analysis showed that at least 50% reduction of KIR3DL2-expressing cells in skin or MRD in blood at week five was associated with numerically higher global ORR and longer PFS (Appendix, page 14). Similar trends were observed on week 14 for MRD and KIR3DL2 expression in both skin and blood compartments (Appendix, page 15).

Discussion

This study evaluated the safety and efficacy of IPH4102 in relapsed/refractory CTCL patients. IPH4102 showed a favourable safety profile and was associated with high rate of durable global response and improvement of QOL in the SS subset, which represented the majority of patients included in this trial.

No DLTs or IPH4102 immune-related AEs were observed and only four patients stopped treatment due to an AE. This compares very favourably to the safety profile of available systemic therapies for CTCL patients. One patient developed a possibly IPH4102-related hepatitis six weeks after treatment discontinuation, which subsequently lead to death. However, this patient had positive viral load of HHV-6B in both serum and liver tissue, which have been previously shown to result in fatal outcomes, particularly in immunocompromised patients[18, 19]. Acknowledging the limited on-treatment liver function changes reported in this study and considering the profile of the included patients being elderly and heavily pre-treated, we believe that the observed hepatic safety profile of IPH4102 is rather reassuring.

Six patients (14%) developed lymphopenia of which 50% were grade 3-4, yet none resulted in opportunistic infections. KIR3DL2 is expressed on around 30% of NK cells[20]; however we did not find that IPH4102 reduces the count of KIR3DL2-expressing NK cells (data not shown). It is

plausible that the observed lymphopenia is a result of IPH4102 reducing the CD4 neoplastic lymphocytosis thus unmasking an underlying lymphopenia caused by the disease, a phenomenon that is common in CTCL[21].

In SS, IPH4102 showed a high global and blood response of 42·9% and 55·9%, respectively. Importantly, these responses were long-lived with median DOR and PFS of approximately one year. Only four out of 35 SS patients experienced progressive disease as best response, which indicates that more than 85% of patients derived benefit. In earlier settings, extracorporeal photopheresis is widely used with an ORR around 43% [22]. More recently, mogamulizumab received regulatory approval in MF/SS patients who received at least one prior systemic therapy, showing a response rate of 37% in the SS subgroup[8]. In the current study, IPH4102 demonstrated highly comparable clinical activity, yet in more refractory patient population with very favourable toxicity profile. Of note, vorinostat is the only FDA-approved agent in managing CTCL patients who have received at least two prior systemic therapies, a population similar to the one treated in the current trial[14]. In a recent phase 3 trial, it showed an ORR of only 2% in SS patients[8]. Thus, the observed clinical activity with IPH4102, if confirmed, could represent a new paradigm shift in managing relapsed/refractory SS patients.

Responses appeared to be restricted to patients without LCT. These results need to be interpreted with caution as only six SS patients had evidence of LCT at baseline. LCT 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 LCT were excluded from the recently reported trial that led to the approval of mogamulizumab in MF/SS patients who received at least one prior systemic therapy[8]. A post-hoc analysis showed that IPH4102 has clinical activity in mogamulizumab pre-treated patients comparable to that observed in the whole population suggesting that prior treatment with mogamulizumab may not affect responses to IPH4102.

Further confirmation of IPH4102 activity in mogamulizumab pre-treated patients in future studies is warranted.

Quality of life represents a major concern for CTCL patients, particulary SS in whom nearly 90% of patients suffer severe debilitating pruritus[4] with profound impact on employment, relationships and social well-being[24]. In the current trial, the majority of included patients experienced marked improvement in various QOL parameters, including itching.

Only eight MF patients were treated in this study, of whom four (50%) had no evidence of KIR3DL2 expression. Thus it is hard to reliably estimate the potential magnitude of benefit of IPH4102 in these patients. Future studies are planned to better characterize the activity of IPH4102 and the value of KIR3DL2 testing in MF patients.

This study has some limitations that should be taken into account. While the observed clinical activity of IPH4102 and its impact on QOL in SS patients is very promising, this study was not powered to provide definite conclusions on these fronts and thus these findings require further confirmation. In addition, we could not draw conclusions on the dose-response relationship as intra-patient dose-escalation took place in the majority of patients in the dose-escalation part of the study.

In conclusion, this study provides preliminary encouraging evidence showing that IPH4102 could emerge as a very promising treatment option in patients with relapsed/refractory SS. Based on these results, the FDA has granted on January 17, 2019 Fast Track designation for IPH4101 in managing these patients. A phase 2 study (TELLOMAK, clinicaltrials.gov: NCT03902184) is currently underway to confirm the clinical activity in SS and evaluate the potential of IPH4102 in other T-cell malignancies that express KIR3DL2.

Contributions

- Martine Bagot, Pierluigi Porcu, Basem William, Maarten Vermeer, Sean Whittaker, and Youn H. Kim formed the safety committee of the study, designed the trial, collected and analysed data in this study, drafted the report, revised it critically, and gave final approval to submit
- Anne Marie-Cardine, Maxime Battistella, Caroline Ram-Wolff, Michael S. Khodadoust and Armand Bensussan, collected data in this study, drafted the report, revised it critically, and gave final approval to submit
- Federico Rotolo, Carine Paturel, Cecile Bonnafous, Helene Sicard, and Hatem A. Azim Jr analysed data in this study, drafted the report, revised it critically, and gave final approval to submit.

Declaration of interests

- Martine Bagot: Travel fees (Kyowa Kirin, Innate Pharma), Investigator (Innate Pharma, Takeda, Kyowa Kirin, Galderma), Speaker bureau (Actelion), Consultant (Innate Pharma, Takeda, Kyowa Kirin, miRagen), Patency (IPH4102).
- Pierluigi Porcu: Investigator (Innate Pharma), Scientific advisor (Innate Pharma), Research support (Kyowa Kirin, Viracta)
- Maxime Battistella: Consultant (Innate Pharma, Bristol-Meyers Squibb, Leo-Pharma), Grant (Takeda)
- Basem M. William: Grant (Innate Pharma), Clinical trial support (Celgene), Advisory board (miRagen)
- Caroline Ram-Wolff: Investigator (Innate Pharma, Kyowa Kirin, Takeda)
- Armand Bensussan: Patency (IPH4102)

- Youn H. Kim: personal fees and grants (Kyowa Kirin), Grants (Merck, Soligenix, Forty-Seven, Neumedicines, Portola Pharma, and Horizon), Personal fees (Eisai, Millennium/Takeda, Seattle Genetics, miRagen, and Innate Pharma)
- Federico Rotolo, Carine Paturel, Cecile Bonnafous, Helene Sicard, and Hatem A. Azim Jr: Employment and possible stock options (Innate Pharma)
- Anne Marie-Cardine, Maarten Vermeer, Sean Whittaker, and Michael S. Khodadoust: no conflicts to declare

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References

1. Criscione VD, Weinstock MA. Incidence of cutaneous T-cell lymphoma in the United States, 1973-2002. Archives of dermatology. 2007; **143**(7): 854-9.

2. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016; **127**(20): 2375-90.

3. Wilcox RA. Cutaneous T-cell lymphoma: 2017 update on diagnosis, risk-stratification, and management. American journal of hematology. 2017; **92**(10): 1085-102.

4. Wright A, Wijeratne A, Hung T, Gao W, Whittaker S, Morris S, et al. Prevalence and severity of pruritus and quality of life in patients with cutaneous T-cell lymphoma. Journal of pain and symptom management. 2013; **45**(1): 114-9.

5. Kubica AW, Davis MD, Weaver AL, Killian JM, Pittelkow MR. Sezary syndrome: a study of 176 patients at Mayo Clinic. Journal of the American Academy of Dermatology. 2012; **67**(6): 1189-99.

6. Alberti-Violetti S, Talpur R, Schlichte M, Sui D, Duvic M. Advanced-stage mycosis fungoides and Sezary syndrome: survival and response to treatment. Clinical lymphoma, myeloma & leukemia. 2015; **15**(6): e105-12.

7. Prince HM, Kim YH, Horwitz SM, Dummer R, Scarisbrick J, Quaglino P, et al. Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial. Lancet. 2017; **390**(10094): 555-66.

8. Kim YH, Bagot M, Pinter-Brown L, Rook AH, Porcu P, Horwitz SM, et al. Mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma (MAVORIC): an international, open-label, randomised, controlled phase 3 trial. The lancet oncology. 2018; **19**(9): 1192-204.

9. Battistella M, Leboeuf C, Ram-Wolff C, Hurabielle C, Bonnafous C, Sicard H, et al. KIR3DL2 expression in cutaneous T-cell lymphomas: expanding the spectrum for KIR3DL2 targeting. Blood. 2017; **130**(26): 2900-2.

10. Hurabielle C, Thonnart N, Ram-Wolff C, Sicard H, Bensussan A, Bagot M, et al. Usefulness of KIR3DL2 to Diagnose, Follow-Up, and Manage the Treatment of Patients with Sezary Syndrome. Clin Cancer Res. 2017; **23**(14): 3619-27.

11. Marie-Cardine A, Viaud N, Thonnart N, Joly R, Chanteux S, Gauthier L, et al. IPH4102, a humanized KIR3DL2 antibody with potent activity against cutaneous T-cell lymphoma. Cancer research. 2014; **74**(21): 6060-70.

12. Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE), v4.03. (https://www .eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_ 5x 7.pd f); June 14, 2010.

13. Olsen EA, Whittaker S, Kim YH, Duvic M, Prince HM, Lessin SR, et al. Clinical end points and response criteria in mycosis fungoides and Sezary syndrome: a consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer. J Clin Oncol. 2011; **29**(18): 2598-607.

14. Olsen EA, Kim YH, Kuzel TM, Pacheco TR, Foss FM, Parker S, et al. Phase IIb multicenter trial of vorinostat in patients with persistent, progressive, or treatment refractory cutaneous T-cell lymphoma. J Clin Oncol. 2007; **25**(21): 3109-15.

15. Chren MM, Lasek RJ, Quinn LM, Mostow EN, Zyzanski SJ. Skindex, a quality-of-life measure for patients with skin disease: reliability, validity, and responsiveness. The Journal of investigative dermatology. 1996; **107**(5): 707-13.

16. Reich A, Heisig M, Phan NQ, Taneda K, Takamori K, Takeuchi S, et al. Visual analogue scale: evaluation of the instrument for the assessment of pruritus. Acta dermato-venereologica. 2012; **92**(5): 497-501.

17. Penel N, Isambert N, Leblond P, Ferte C, Duhamel A, Bonneterre J. "Classical 3 + 3 design" versus "accelerated titration designs": analysis of 270 phase 1 trials investigating anti-cancer agents. Investigational new drugs. 2009; **27**(6): 552-6.

18. Charnot-Katsikas A, Baewer D, Cook L, David MZ. Fulminant hepatic failure attributed to infection with human herpesvirus 6 (HHV-6) in an immunocompetent woman: A case report and review of the literature. Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology. 2016; **75**: 27-32.

19. Hill JA, Myerson D, Sedlak RH, Jerome KR, Zerr DM. Hepatitis due to human herpesvirus 6B after hematopoietic cell transplantation and a review of the literature. Transplant infectious disease : an official journal of the Transplantation Society. 2014; **16**(3): 477-83.

20. Chan AT, Kollnberger SD, Wedderburn LR, Bowness P. Expansion and enhanced survival of natural killer cells expressing the killer immunoglobulin-like receptor KIR3DL2 in spondylarthritis. Arthritis and rheumatism. 2005; **52**(11): 3586-95.

21. Yawalkar N, Ferenczi K, Jones DA, Yamanaka K, Suh KY, Sadat S, et al. Profound loss of T-cell receptor repertoire complexity in cutaneous T-cell lymphoma. Blood. 2003; **102**(12): 4059-66.

22. Zic JA. The treatment of cutaneous T-cell lymphoma with photopheresis. Dermatologic therapy. 2003; **16**(4): 337-46.

23. Scarisbrick JJ, Prince HM, Vermeer MH, Quaglino P, Horwitz S, Porcu P, et al. Cutaneous Lymphoma International Consortium Study of Outcome in Advanced Stages of Mycosis Fungoides and Sezary Syndrome: Effect of Specific Prognostic Markers on Survival and Development of a Prognostic Model. J Clin Oncol. 2015; **33**(32): 3766-73.

24. Demierre MF, Gan S, Jones J, Miller DR. Significant impact of cutaneous T-cell lymphoma on patients' quality of life: results of a 2005 National Cutaneous Lymphoma Foundation Survey. Cancer. 2006; **107**(10): 2504-11.

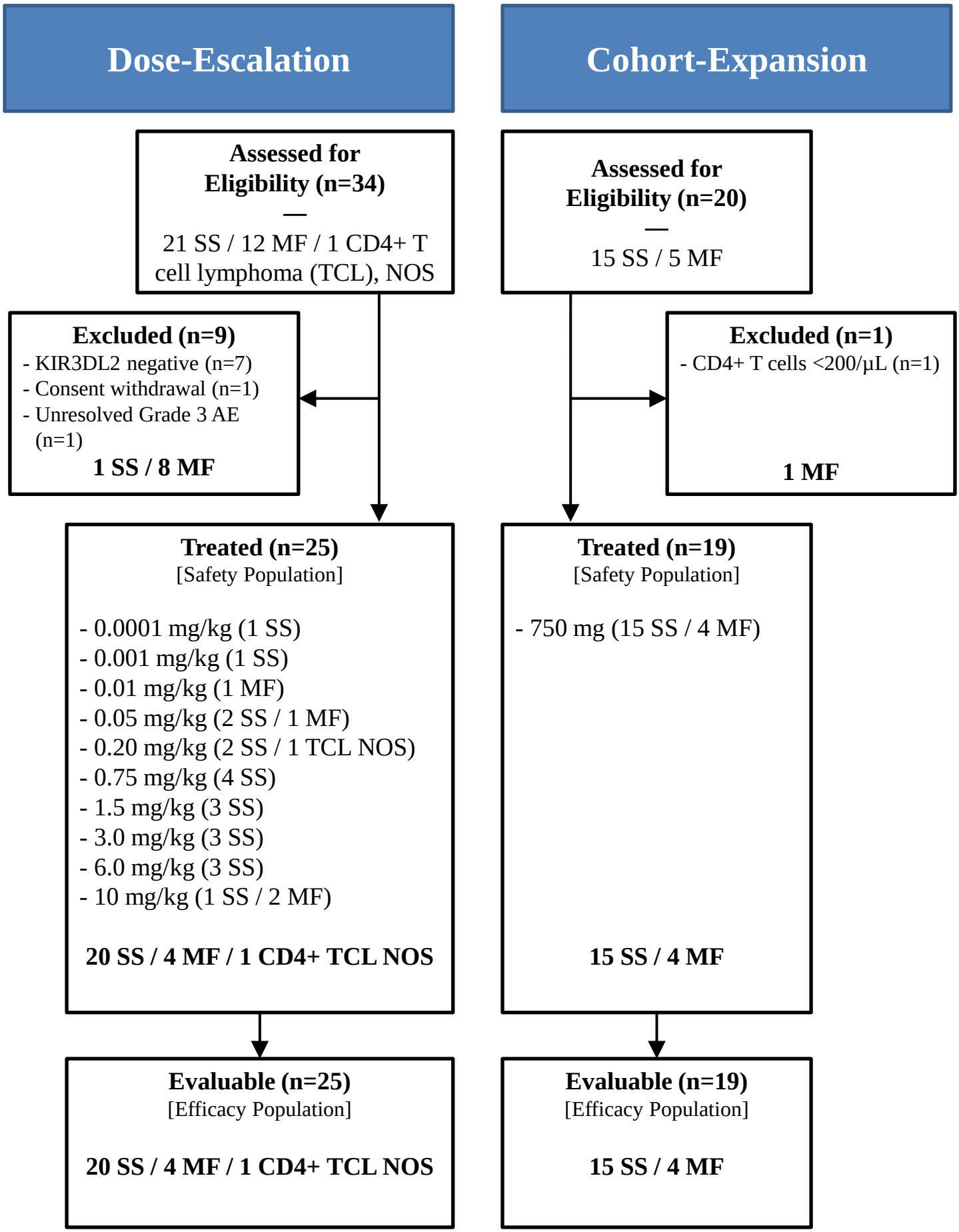
Figure legends

Figure 1: Study flow chart

Figure 2: Clinical activity of IPH4102 in patients with Sézary Syndrome (N=35). **A:** Waterfall plot showing the best change in mSWAT from baseline. Colours represent best global response: CR (complete response) in dark green, PR (partial response) in light green, SD (stable disease) in blue and PD (progressive disease) in red. **B:** Swimmer plot showing individual patients and their duration of response. Colours represent the global response assessed. C: Kaplan Meier estimate of the progression-free survival with 95% confidence interval. N is the number of patients still at risk, (C) is the cumulative number of censored patients.

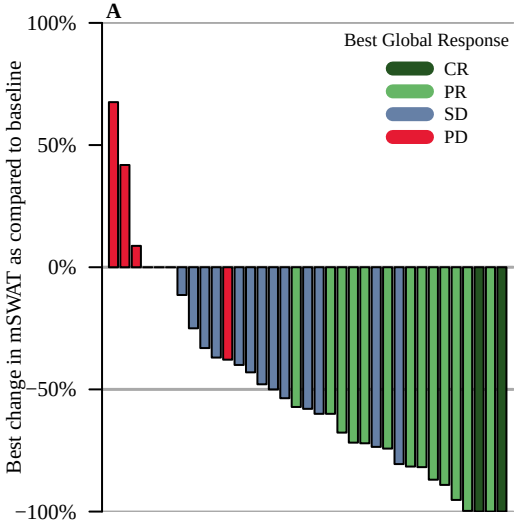
Figure 3: Impact of IPH4102 on quality of life of all patients included in the trial (N=44). **A:** Median Visual Analogue Scale (VAS) scores. **B:** Median SkinDex29 global scores. C: Median SkinDex29 symptoms scores. D: Median SkinDex29 emotions scores. E: Median SkinDex29functional scores. The x-axis indicates time of IPH4102 administration in months and the number of patients evaluable per time-point. The dotted lines represent the standard deviation.

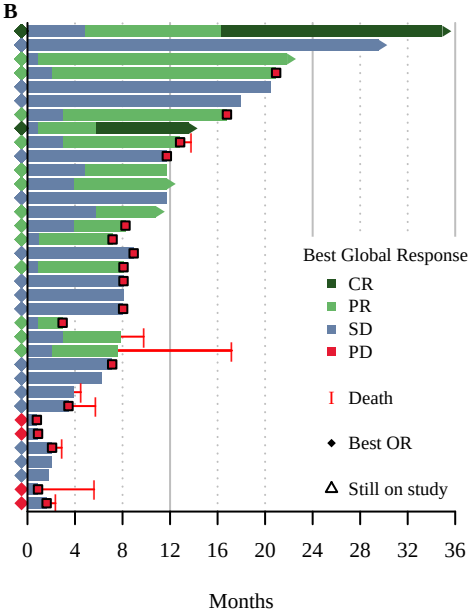
Figure 4: A: Mean count of Aberrant Sézary cells ($CD7^-$ or $CD26^-$ $CD4^+$) per µL blood, throughout treatment, identified by multicolour flow cytometry in patients in global PR or CR (green), SD (blue) or PD (red). **B:** Mean count of KIR3DL2+ CD4 T cells per µL blood, throughout treatment, identified by multicolour flow cytometry in patients in global PR or CR (green), SD (blue) or PD (red). The x-axis indicates the weeks of IPH4102 administration and the number of patients evaluable per time-point in each response category. The dotted lines represent the standard deviation.



SS: Sézary Syndrome; MF: Mycosis Fungoides; NOS: Not Otherwise Specified

Figure 2


A
100%
50%
0%
−50%
−100%
Best change in mSWAT as compared to baseline
Best Global Response
CR
PR
SD
PD


B
Best Global Response
CR
PR
SD
PD
Death
Best OR
Still on study
0
4
8
12
16
20
24
28
32
36
Months

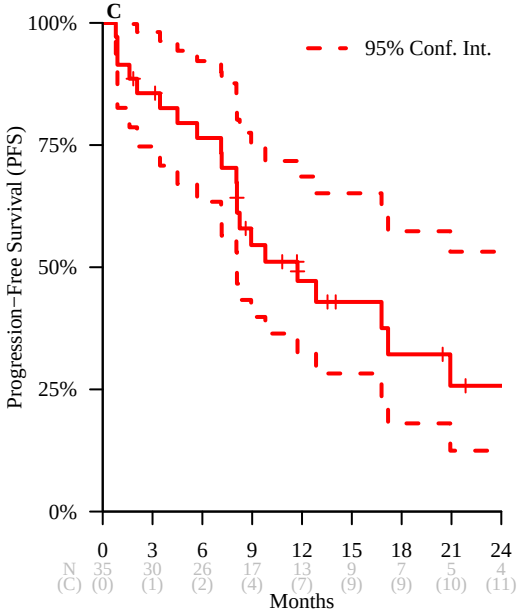

C
100%
75%
50%
25%
0%
Progression−Free Survival (PFS)
95% Conf. Int.
0
3
6
9
12
15
18
21
24
N
35
30
26
17
13
9
7
5
4
(C)
(0)
(1)
(2)
(4)
(7)
(9)
(9)
(10)
(11)
Months

Figure 3

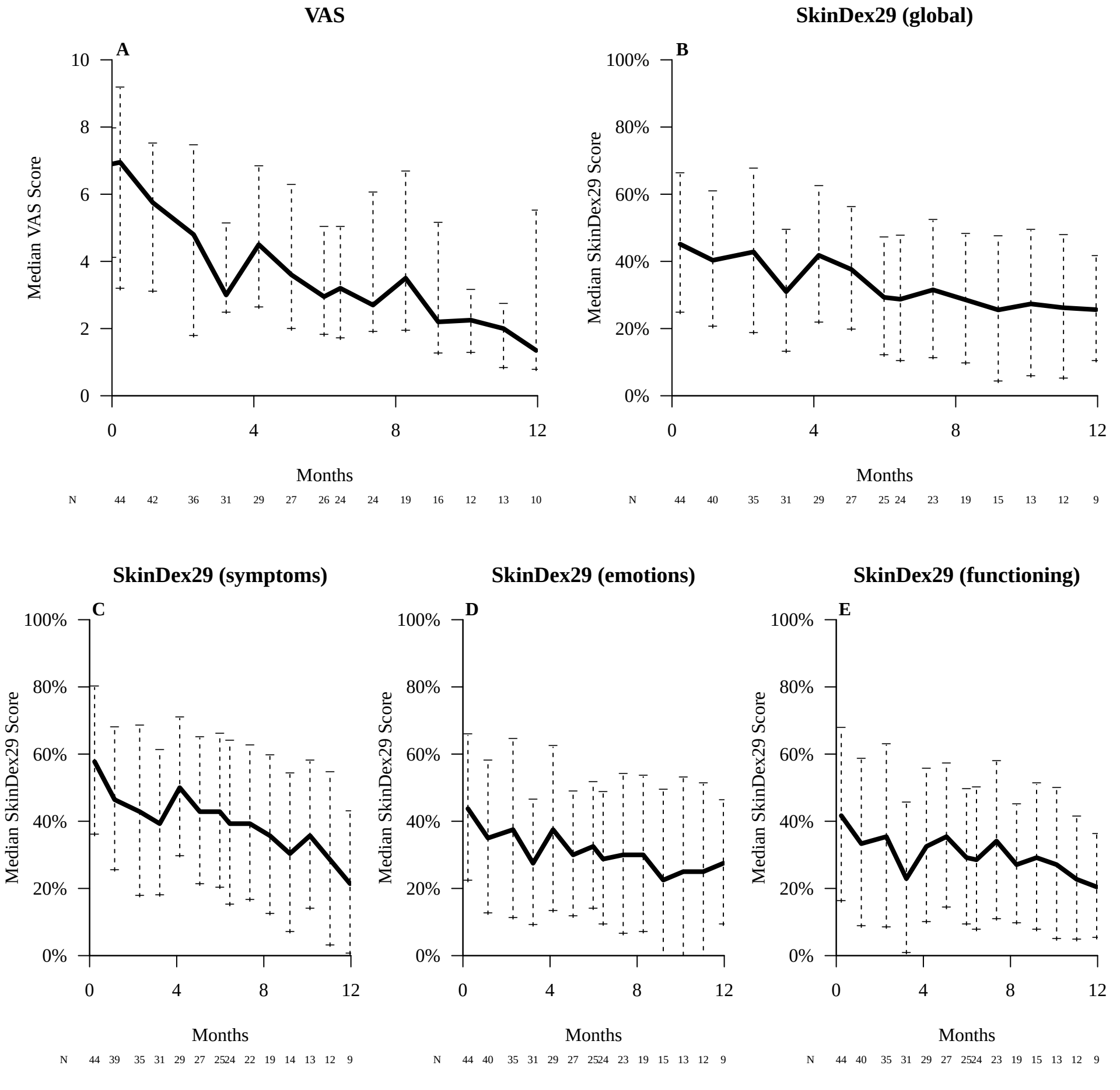
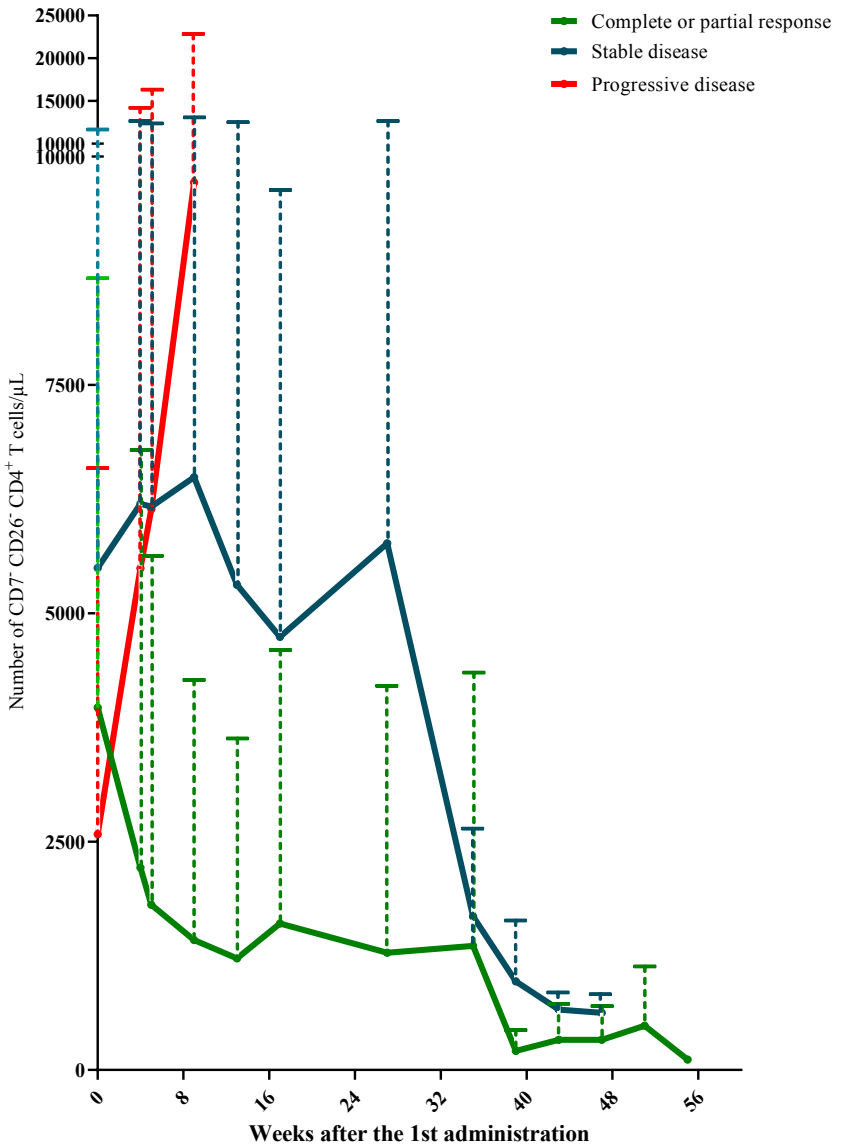
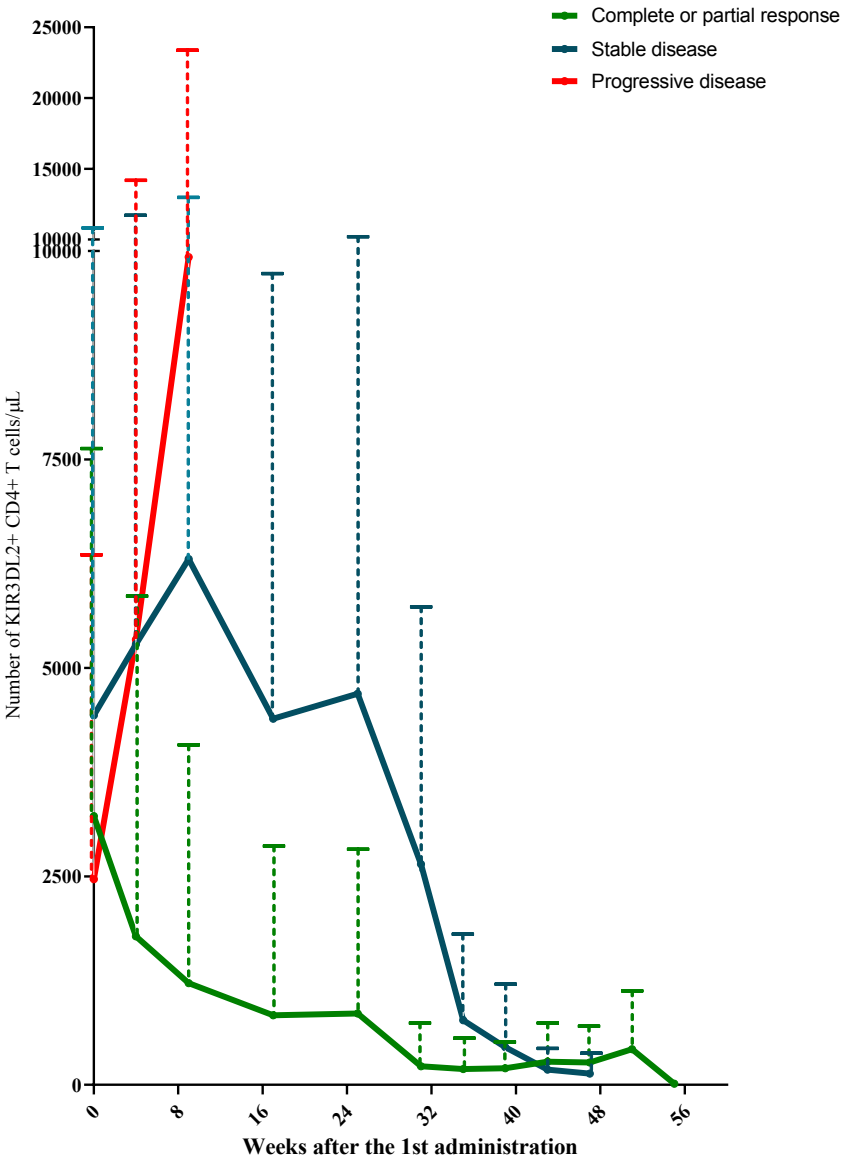

VAS
A
Median VAS Score
10
8
6
4
2
0
0
4
8
12
Months
N 44 42 36 31 29 27 26 24 24 19 16 12 13 10
SkinDex29 (global)
B
Median SkinDex29 Score
100%
80%
60%
40%
20%
0%
0
4
8
12
Months
N 44 40 35 31 29 27 25 24 23 19 15 13 12 9
SkinDex29 (symptoms)
C
Median SkinDex29 Score
100%
80%
60%
40%
20%
0%
0
4
8
12
Months
N 44 39 35 31 29 27 25 24 22 19 14 13 12 9
SkinDex29 (emotions)
D
Median SkinDex29 Score
100%
80%
60%
40%
20%
0%
0
4
8
12
Months
N 44 40 35 31 29 27 25 24 23 19 15 13 12 9
SkinDex29 (functioning)
E
Median SkinDex29 Score
100%
80%
60%
40%
20%
0%
0
4
8
12
Months
N 44 40 35 31 29 27 25 24 23 19 15 13 12 9

Figure 4



Weeks	0	4	9	17	25	31	35	39	43	47	51	55
Complete or partial response (N)	15	15	12	12	13	7	8	3	3	3	3	2
Stable disease (N)	15	13	10	11	7	5	5	3	3	2	0	0
Progressive disease (N)	4	3	2	0	0	0	0	0	0	0	0	0



Weeks	0	4	9	17	25	31	35	39	43	47	51	55
Complete or partial response (N)	15	15	12	12	13	7	8	3	3	3	3	2
Stable disease (N)	15	13	10	11	7	5	5	3	3	2	0	0
Progressive disease (N)	4	3	2	0	0	0	0	0	0	0	0	0

Table 1: Patients' characteristics

	Dose escalation (N=25)	**Cohort expansion (N=19)**	**SS patients (N=35)***
Age			
- Median (IQR), in 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			
- MF	4 (16%)	4 (21%)	NA
- SS	20 (79%)	15 (79%)	35 (100%)
- CD4+ T cell lymphoma, NOS	1 (5%)	0	NA
Evidence of large cell transformation according to central evaluation	7 (28%)	5 (26%)	6 (17%)
Clinical stage at study entry (MF/SS)			
- IB	1 (4%)	1 (5%)	1 (3%)^
- IIB	3 (12%)	3 (16%)	0
- IIIA	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%)

Median (IQR) time from initial CTCL diagnosis to starting IPH4102, in 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 and/or blood	25 (100%)	13 (68%)	33 (94%)
N of systemic therapy received			
- Median (IQR)	4 (2 – 6)	2 (2 – 4)^^	2 (2 – 4)
Prior treatment with			
- Bexarotene	20 (80%)	11 (58%)	24 (69%)
- Methotrexate	17 (68%)	8 (42%)	19 (54%)
- Interferon alpha	12 (48%)	9 (47%)	16 (46%)
- HDAC inhibitors**	9 (36%)	9 (47%)	13 (37%)
- Extracorporeal photopheresis	11 (44%)	6 (32%)	17 (49%)
- Gemcitabine	6 (24%)	4 (21%)	7 (20%)
- Mogamulizumab	7 (28%)	2 (11%)	7 (20%)
- Brentuximab vedotin	3 (12%)	1 (5%)	2 (6%)

IQR: interquartile range, SS: Sézary Syndrome, MF: Mycosis Fungoides, NOS: not otherwise specified,

N: Number, NA: not applicable

* Patients included in both dose-escalation and cohort-expansion parts

** Romidepsin and /or vorinostat

^ One patient had history of being stage IVB SS but had limited blood involvement at study entry (B1). As per protocol, patient was considered as SS

^^ One patient had a protocol violation, received only one line of prior systemic therapy

Table 2: Summary of adverse events (AEs) occurring in at least 10% of patients and all grade 3-5 AEs

	All adverse events			**Possibly related adverse events***		
	Grade 1-2	**Grade 3**	**Grade 4**	**Grade 1-2**	**Grade 3**	**Grade 4**
Peripheral oedema	12 (27%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)
Asthenia	9 (20%)	0 (0%)	0 (0%)	5 (11%)	0 (0%)	0 (0%)
Fatigue	9 (20%)	0 (0%)	0 (0%)	3 (7%)	0 (0%)	0 (0%)
Cough	7 (16%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Pyrexia	7 (16%)	0 (0%)	0 (0%)	3 (7%)	0 (0%)	0 (0%)
Diarrhoea	7 (16%)	0 (0%)	0 (0%)	2 (5%)	0 (0%)	0 (0%)
Arthralgia	7 (16%)	0 (0%)	0 (0%)	2 (5%)	0 (0%)	0 (0%)
Lymphopenia	3 (7%)	3 (7%)	0 (0%)	3 (7%)	3 (7%)	0 (0%)
Fall	6 (14%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Headache	6 (14%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)
Hypertension	3 (7%)	2 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Anaemia	4 (9%)	1 (2%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)
Constipation	5 (11%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)
Dyspnoea	5 (11%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)
Chills	5 (11%)	0 (0%)	0 (0%)	3 (7%)	0 (0%)	0 (0%)
Rash	3 (7%)	1 (2%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)
Confusional state	1 (2%)	1 (2%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)
Malaise	2 (5%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Pain of skin	2 (5%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Staphylococcal sepsis	0 (0%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)
Acute kidney injury	1 (2%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)
Tremor	1 (2%)	1 (2%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)
Dysphagia	1 (2%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Delirium	1 (2%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Fulminant hepatitis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Acute respiratory failure	0 (0%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)
Sepsis	0 (0%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	1 (2%)
Postoperative	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

wound infection						
Squamous cell carcinoma of lung	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hypoalbuminaemia	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Transaminase increase	0 (0%)	1 (2%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)
Hip fracture	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hallucination	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hypotension	0 (0%)	1 (2%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)

*Possibly-related AE as defined by the treating investigator

** Including one grade 5 AE