# Open label, multicenter phase I study of IPH4102, a humanized anti-KIR3DL2 monoclonal antibody, in patients with relapsed/refractory cutaneous T-cell lymphomas (CTCL)

Published: 05-08-2015
Last updated: 19-04-2024

Primary Objective:To assess the safety and tolerability of increasing intravenous (IV) doses of single agent IPH4102 administered to patients with relapsed/refractory CTCL by:_characterizing the dose limiting toxicities (DLT) and (S)AEs...

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|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Lymphomas non-Hodgkin's T-cell |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON44047

**Source**
ToetsingOnline

**Brief title**
IPH4102CTCL

### Condition

- Lymphomas non-Hodgkin's T-cell

**Synonym**
Cutaneous T-cell lymphoma; Malignancy of immune cells in the skin

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Innate Pharma
**Source(s) of monetary or material Support:** Innate Pharma SA

## Intervention

**Keyword:** anti-KIR3DL2, cutaneous T-cell lymphomas (CTCL), Innate IPH4102

## Outcome measures

**Primary outcome**

1. Occurrence of DLT

DLT is defined as the occurrence of any

_grade *3 non hematologic or hematologic toxicity lasting for *8 days, except

lymphopenia, or

_grade *4 symptoms judged to be consistent with an Infusion Related Reaction

(IRR)/cytokine release syndrome without premedication or

_grade *3 symptoms judged to be consistent with recurrent IRR/cytokine release

syndrome despite premedication or

_grade *3 tumor lysis syndrome

MTD will be defined as the highest dose level where none out of 3 or no more

than 1 out of 6 patients experiences a DLT within 14 days after first IPH4102

administration

2. Occurrence of Adverse Events (AEs) and Serious Adverse Events (SAEs)

Safety of IPH4102 is assessed using the CTCAE grading system (version 4.03 of

June 14, 2010) and coded according to MedDra.

A Safety Committee will evaluate the safety data in the dose escalation portion

and during the cohort expansion portion.

**Secondary outcome**

Safety endpoints:

_Adverse Events (AEs)

_Serious Adverse Events (SAEs)

_Drug related AEs

_Drug related SAEs

Efficacy endpoints:

_Overall Objective Response Rate (complete response (CR) + partial response (PR))

_Response (CP/PR) duration

_Progression-free survival (PFS)

Response assessment will be performed according to the Global Response Score of the International Society for Cutaneous Lymphomas/European Organization of Research and Treatment of Cancer (ISCL/EORTC) criteria for MF/SS. Cutaneous involvement will be assessed with the Modified Severity Weighed Assessment Tool (mSWAT) or for subcutaneous tumors by appropriate imaging. Independent confirmation of the response may be requested by the Sponsor.

_Pruritus severity changes

For pruritus assessment a visual analogue scale (VAS) and a standardized skin-specific questionnaire (SkinDex29) will be used.

PK endpoints:

_Maximum and trough concentration of IPH4102 at each administration

_Area under the curve from time 0 to day 7 (AUC day 0-7) for the first and

fourth administration

_Accumulation index (in terms of ratio of Cmax and of AUC 0-7 days between the

fourth and first administration)

_Presence of Human Anti-Drug Antibodies (ADAs) and if present, assessment of

their neutralizing potential.

# Study description

**Background summary**

The extracellular receptor KIR3DL2 has emerged as one of the most consistent markers of CTCL cells, especially in Sézary syndrome (SS), transformed mycosis fungoides (tMF) and CD30+ lymphoproliferative disorders (LPD, Anaplastic Large Cell Lymphoma (ALCL) subtype). On normal cells, KIR3DL2 is expressed on minor subsets of lymphocytes, but is absent from any other human tissue.
IPH4102 is a humanized IgG1, Fc-enhanced monoclonal antibody (mAb) directed against the human protein KIR3DL2. IPH4102 is selected and designed to deplete effectively KIR3DL2-expressing cells, mainly by antibody-dependent cell-mediated cytotoxicity (ADCC).

**Study objective**

Primary Objective:
To assess the safety and tolerability of increasing intravenous (IV) doses of single agent IPH4102 administered to patients with relapsed/refractory CTCL by:
_characterizing the dose limiting toxicities (DLT) and (S)AEs and
_identifying a MTD or determine a dose for further studies (RP2D)

Secondary Objectives:
_To explore antitumor activity
_To assess pharmacokinetics (PK)
_To assess immunogenicity
_To explore pruritus

Other Objectives:
_To assess cytokine release

_To explore pharmacodynamics in the peripheral blood, in skin lesions and lymph nodes
_To explore NK cell and macrophage infiltration in skin lesions
_To assess expression of immune receptors other than KIR3DL2 in skin lesions
_To assess Minimal Residual Disease (MRD)
_At specific sites: To explore blood NL cell function

## Study design

Overall Design:
This first in human dose-finding study consists of two sequential study portions:
a) A dose escalation portion identifying the Maximum Tolerated Dose (MTD)/ Recommended Phase 2 Dose (RP2D) and
b) A cohort expansion portion that further characterizes the MTD/RP2D
In both study portions patients with KIR3DL2-expressing relapsed/refractory CTCL will be eligible. In the cohort expansion portion enrolment in two CTCL subtype-specific cohorts is planned. Based on pre-clinical data these cohorts may include the CTCL subtypes tMF and SS. Patients will remain on treatment until disease progression, unacceptable toxicity or consent withdrawal. Patients will be followed for survival status and subsequent anti-neoplastic therapies for 12 months after end of treatment visit or until End of Study for whatever reason.

Planned treatment schedule:
Similar treatment schedules are currently planned to be used in the two study portions. Patients will receive 4 x qw IPH4102 administrations. Patients who show a clinical benefit at the first scheduled response assessment may receive further treatment. Additional 10 administrations every other week followed by treatments every 4 weeks until progression or treatment discontinuation for any other reason will be allowed. An alternative treatment schedule might be used in the cohort expansion portion adapted according to emerging information from the dose escalation portion.

## Intervention

Enrolment of approximately 60 patients with KIR3DL2-positive CTCL in two sequential study portions:
_dose-escalation portion: sequential enrolment of approximately 40 CTCL patients in 10 Dose cohorts (0.0001; 0.001; 0.010; 0.050; 0.200; 0.750; 1.5; 3.0; 6.0; 10.0 mg/kg)
_cohort expansion portion: enrolment of 2 x 10 patients in 2 CTCL subtype cohorts emerging from the dose escalation portion (expected: SS and tMF)

## Study burden and risks

Risks: possible side effects of the study drug. Burden: Physical examinations, vital functions examinations, ECGs, bloodtests, questionnaires, photo's of the skin.

The patient can continue the treatment until progression of the disease or unacceptable toxicity.

# Contacts

**Public**
Innate Pharma

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FR
**Scientific**
Innate Pharma

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FR

# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

Note: In the dose escalation portion, all subtypes of relapsed/refractory CTCL will be allowed, in the cohort expansion portion inclusion of specific CTCL subtypes is planned according to findings of the dose escalation portion (e.g. tMF and SS).
1) Patients with relapsed/refractory, biopsy-proven primary cutaneous T-cell lymphoma who

have
received at least two previous standard systemic therapies and, if MF/SS, is stage IBIVB at study entry. Total skin electron beam irradiation is not regarded as systemic therapy.
2) Centrally assessed KIR3DL2 expression on tumor cells. A blood sample and skin biopsies will be obtained within 4 weeks of beginning study medication, for assessment of KIR3DL2 by flow cytometry or immunohistochemistry (IHC). KIR3DL2 expression on *5% malignant cells in skin or on *5% malignant cells in blood (Immunophenotype: CD3+CD4+CD8-) is regarded as KIR3DL2 positive. If a patient has different lesion morphology (patch, plaque, tumor), a biopsy will be obtained from each morphologic lesion and KIR3DL2-positivity in at least one lesion will be sufficient for enrolment of a patient.
3) Patients must have the following minimum wash-out from previous treatments:
- *12 weeks for total skin electron beam irradiation,
- *4 weeks for monoclonal antibodies (* 8 weeks for alemtuzumab),
- *3 weeks for local radiation therapy, systemic cytotoxic anticancer therapy, treatment with other anti-neoplastic investigational agents,
- *3 weeks for systemic retinoids, interferons, vorinostat, romidepsin, fusion proteins,
- *3 weeks for phototherapy,
- *2 weeks for topical therapy (including steroids, retinoids, nitrogen mustard or imiquimod). Topical steroids (maximum strength: Class III according to World Health Organization Classification of Topical Corticosteroids) and/or oral
steroids (* 10 mg prednisone equivalent/day) are allowed, if the patient has been on a stable dose with stable disease for at least 1 month prior to study entry.
4) At least 18 years of age.
5) ECOG performance status of * 2.
6) Adequate baseline laboratory data: hemoglobin >9 g/dL, absolute neutrophil count (ANC) *1,000/*L, CD4+ T-cells *200/*l, platelets *50,000/*L, bilirubin *1.5 X upper limit of normal (ULN) or *3 X ULN for patients with Gilbert's disease, serum creatinine *1.5 X ULN, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) *3 X ULN.
7) Women of childbearing potential (WOCBP) must have a negative serum beta-HCG pregnancy test result within seven days of treatment and must practice an effective method of contraception during treatment and for at least 9 months (270 days) following the last dose of study drug.
8) Female patients who are post-menopausal or surgically sterile.
9) Male patients who agree to practice effective barrier contraception.
10) Ability to understand and the willingness to sign a written informed consent document.
11) No psychological, familial, sociological, or geographical condition potentially hampering compliance with the study protocol and follow-up schedule.

## Exclusion criteria

1) Patients with limited disease (if MF/SS: stages IA), or central nervous system (CNS) disease.

2) Clinical relevant AEs or laboratory results related to previous anti-neoplastic therapy have not resolved to a NCI-CTCAE grade *1.
3) Concomitant corticosteroid use, systemic or topical, for treatment of skin disease. However, topical steroids (maximum strength: Class III according to World Health Organization Classification of Topical Corticosteroids) and/or oral steroids (*10 mg prednisone equivalent/day) are allowed, if patient has been on a stable dose with stable disease for at least 4 weeks prior to study entry.
4) Patients who have undergone major surgery < 4 weeks prior to starting study drug
5) Patients who have undergone a stem cell transplantation
6) Patients with known NCI CTCAE Grade 3 or higher (requiring IV antibiotics) active systemic or cutaneous viral, bacterial, or fungal infection.
7) Patients who are Hepatitis B or Hepatitis C antibody positive.
8) Patients who are known to be HIV-positive.
9) Prior hypersensitivity reaction to monoclonal antibodies, other therapeutic proteins, or immunotherapy.
10) Patients with a history of other malignancies during the past three years. (The following are exempt from the three-year limit: non-melanoma skin cancer, Lymphomatoid papulosis, curatively treated localized prostate cancer, curatively treated localized breast cancer, resected thyroid cancer, cervical intraepithelial neoplasia or cervical carcinoma in situ on biopsy).
11) Patients who are currently pregnant or breastfeeding.
12) Patients with congestive heart failure, Class III or IV, by New York Heart Association (NYHA) criteria.
13) Patients with any serious underlying medical condition that would impair their ability to receive or tolerate the planned treatment.
14) Patients with dementia or altered mental status that would preclude understanding and rendering of informed consent document.

# Study design

## Design

**Study type:** Interventional

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|---|---|
| Masking: | Open (masking not used) |
| Control: | Uncontrolled |
| Primary purpose: | Treatment |

## Recruitment

NL

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|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 22-11-2016 |

| | |
|---|---|
| Enrollment: | 6 |
| Type: | Actual |

### Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | IPH4102 |
| Generic name: | IPH4102 |

## Ethics review

| | |
|---|---|
| Approved WMO Date: | 05-08-2015 |
| Application type: | First submission |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden)<br>metc-ldd@lumc.nl |

| | |
|---|---|
| Approved WMO Date: | 19-07-2016 |
| Application type: | First submission |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden)<br>metc-ldd@lumc.nl |

| | |
|---|---|
| Approved WMO Date: | 23-09-2016 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden)<br>metc-ldd@lumc.nl |

| | |
|---|---|
| Approved WMO Date: | 09-11-2016 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden)<br>metc-ldd@lumc.nl |

Approved WMO

| | |
|---|---|
| Date: | 02-05-2017 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |
| | metc-ldd@lumc.nl |

Approved WMO

| | |
|---|---|
| Date: | 11-07-2017 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |
| | metc-ldd@lumc.nl |

Approved WMO

| | |
|---|---|
| Date: | 10-08-2017 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |
| | metc-ldd@lumc.nl |

Approved WMO

| | |
|---|---|
| Date: | 17-10-2017 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |
| | metc-ldd@lumc.nl |

Approved WMO

| | |
|---|---|
| Date: | 18-10-2017 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |
| | metc-ldd@lumc.nl |

Approved WMO

| | |
|---|---|
| Date: | 01-12-2017 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |
| | metc-ldd@lumc.nl |

Approved WMO

| | |
|---|---|
| Date: | 21-02-2018 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |
| | metc-ldd@lumc.nl |

Approved WMO

| | |
|---|---|
| Date: | 19-04-2018 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |
| | metc-ldd@lumc.nl |

Approved WMO

| | |
|---|---|
| Date: | 23-04-2018 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |
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Approved WMO

| | |
|---|---|
| Date: | 01-08-2018 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |
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Approved WMO

| | |
|---|---|
| Date: | 01-11-2018 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |
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Approved WMO

| | |
|---|---|
| Date: | 27-11-2019 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |
| | metc-ldd@lumc.nl |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| EudraCT | EUCTR2015-000260-34-NL |
| CCMO | NL53824.058.15 |

# Study results

Date completed: 27-11-2018

Results posted: 14-04-2021

Actual enrolment: 3

**First publication**
07-04-2021