# Phase I/Ib, open-label, multiple ascending dose, first-in-human study, to investigate the safety, pharmacokinetics, pharmacodynamics and preliminary efficacy of INT-1B3 in patients with advanced solid tumors

Published: 06-01-2020
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Primary Objectives:Phase 1/ Dose escalation:• To determine the safety and tolerability of INT-1B3, administered as single agent by 120-min i.v. infusion• To identify the Recommended Phase 2 Dose (RP2D) of INT-1B3 Phase 1b/ Dose expansion:• To...

| | |
|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Pending |
| **Health condition type** | Miscellaneous and site unspecified neoplasms benign |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON52968

**Source**
ToetsingOnline

**Brief title**
INT-1B3

### Condition

- Miscellaneous and site unspecified neoplasms benign

**Synonym**
Advanced solid tumors

**Research involving**

Human

## Sponsors and support

**Primary sponsor:** InteRNA Technologies B.V.
**Source(s) of monetary or material Support:** InteRNA Technologies B.V.

## Intervention

**Keyword:** Advanced Solid Tumors, First-in-Human Study, INT-1B3, Phase I/Ib

## Outcome measures

### Primary outcome

Primary End Points:

• Incidence of adverse events (AEs) and serious AEs (SAEs) according to National Cancer Institute (NCI) - Common Terminology Criteria for Adverse Events (CTCAE) criteria v5.0, dose limiting toxicities (DLTs), AEs leading to discontinuation, deaths, electrocardiogram (ECG) abnormalities, and clinically significant laboratory abnormalities)

• RP2D will be based on DLTs, the Maximum Tolerated Dose (MTD), and all available safety, PK/PD, and efficacy parameters

### Secondary outcome

Secondary End Point:

• The plasma concentration-time profile of INT-1B3 and the derived PK parameters (e.g., area under the curve [AUC], peak plasma concentration [Cmax], time to reach Cmax [tmax], terminal elimination rate constant [Lambda z])

• Objective response rate (ORR), duration of response (DOR), and clinical benefit rate (CBR), Progression Free Survival (PFS)

Exploratory endpoints:

• Correlation/measure of association of plasma PK and various PD biomarkers in the peripheral blood

• Change from baseline in expression of target mRNAs in white blood cells and other pharmacodynamic biomarkers in blood samples at each dose level

• Change from baseline in exploratory biomarkers in tumor biopsies and in plasma samples

• Summary measures of antitumor activity by pre-treatment level of biomarkers of interest; correlation/measure of association of antitumor activity and change (or percent change) from baseline in biomarkers of interest

• Anti-PEG antibodies

• ORR, DOR, CBR, PFS (iRECIST)

# Study description

### Background summary

The trial drug, INT-1B3, is a microRNA (miRNA) therapeutic. A miRNA is a copy of a naturally occurring molecule in the human body, this one is called miR-193a-3p. The miRNA is covered with a lipid, forming INT-1B3. The covering lipid enables the molecule to be efficiently delivered to the cancer cells. Laboratory experiments have shown that the trial drug has a function in killing cancer cells. In several cancers it is found that the amount of miR-193a-3p, is lower than in normal cells. By administering INT-1B3, we aim to increase the amount of miR-193a-3p in the cells and we expect that the trial drug will have an anti-cancer effect. In addition, we expect that INT-1B3 activates the immune system to recognize and kill cancer cells.

### Study objective

Primary Objectives:
Phase 1/ Dose escalation:
• To determine the safety and tolerability of INT-1B3, administered as single

agent by 120-min i.v. infusion
• To identify the Recommended Phase 2 Dose (RP2D) of INT-1B3

Phase 1b/ Dose expansion:
• To confirm the safety/tolerability and the RP2D of INT-1B3

Secondary Objectives:
• To characterise the plasma pharmacokinetics (PK) of INT-1B3
• To provide a preliminary estimate of efficacy of INT-1B3 according to standard criteria by response evaluation criteria in solid tumors (RECIST) v1.1 or modified RECIST (mRECIST)

Exploratory Objectives:
• To determine the pharmacodynamic (PD) activity (i.e., target engagement) of INT-1B3 in blood cells
• To determine other exploratory PD markers in pre- and on-treatment tumor biopsies (expansion cohort only) and plasma samples
• To assess production of anti-polyethylene glycol (PEG) antibodies
• To provide a preliminary estimate of efficacy of INT-1B3 according to standard criteria by immune RECIST (iRECIST)

**Study design**

This is a two-part, multi-center, open-label, multiple ascending doses, First-in-Human clinical study to evaluate the safety, PK, PD, and preliminary efficacy of INT-1B3 in the treatment of patients with advanced solid tumors.

Dose escalation phase (Phase I)
This Phase I study follows a *hybrid* 3+3 study design in *all-comers* cancer patients enrolled and treated in cohorts.
Each patient will be observed for a minimum of 21 days (DLT observation period and cycle duration) before the next cohort is enrolled and may begin to receive study drug.
In order to limit exposure of too many patients to biologically irrelevant doses of INT-1B3, dose escalation started with 1 patient per cohort, and escalated with 1 patient per cohort until AE of Grade >= 2 is observed. Then, the dose escalation continues with a classical 3+3 design.

In addition, as soon as the next dose level planned, is equal or above the human equivalent dose (HED; >=0.1 mg/kg) of the no adverse event level (NOAEL) in NHP, at least 3 patients will be included in that and further cohorts.

As a safety precaution, in a cohort of 3 patients, an initial sentinel patient in each cohort will receive INT-1B3 and will be observed for a period of one week prior to additional patients in the cohort being dosed.
If no DLT is observed, then escalation to the next dose level can take place.
If one out of three patients experiences a DLT, then up to a total of six

evaluable patients will be enrolled at the current dose level. Escalation will occur if no additional DLTs are seen in that cohort.
If 2 or more treated patients at a dose level experience a DLT during the DLT period, enrollment at that dose and dose escalation will stop.
If 6 patients were already treated at the prior lower dose level, then this lower dose will be considered the MTD. In case only 3 patients have been treated at that prior lower dose level, then 3 more patients will be enrolled.
If no DLT occurs at any of the dose levels tested, a RP2D of INT-1B3 will be declared, if deemed appropriate, based on all available safety, PK/PD and efficacy data.
For the dose escalation phase (i.e., sufficient and rapid patient recruitment), a fourth patient can be included per dose level to compensate for early dropouts.

Per protocol v7.0, once-weekly dosing cohorts will be added in addition to the twice-weekly cohorts following the same 3+3 design to define the RP2D. Inclusion of patients into a twice-weekly or once-weekly cohort will be at investigator*s discretion. A separate RP2D will be established for the twice-weekly (RP2Dbiw) and once-weekly dosing (RP2Donce).

Expansion cohorts (Phase Ib)
Upon completion of the dose escalation phase of the study, up to 60 patients will be enrolled to further confirm the safety, tolerability, and preliminary efficacy of the RP2D in two expansion cohorts. Patients with HCC (n=30) and TNBC (n=30) will be enrolled to receive INT-1B3 at the RP2D.
Patients who enter the study in the expansion phase will be randomized to receive INT-1B3 either once-weekly at the RP2Donce continuously or twice-weekly at the RP2Dbiw for one cycle alternated with 3 cycles once-weekly at the RP2Donce via 120-min i.v. infusions.
For both the dose escalation and dose expansion parts of the study, patients will continue to receive INT-1B3 until PD, death, unacceptable toxicity or withdrawal of consent. Patients will be observed for safety in a 30-day follow-up period after last treatment.
The dose-escalation process and expansion phase will be monitored by a Cohort Review Committee (CRC)

**Intervention**

The patients will receive INT-1B3 via an intravenous infusion for 120 minutes per treatment. They will receive treatment once or twice per week, in 21-day cycles.

**Study burden and risks**

The evaluation of risk is based on information obtained from the ongoing clinical study and non-clinical studies in animals, and potential effects based

on the proposed mechanism of action (MOA) and experience with similar compounds.
Possible negative effects of INT-1B3 could be:
- due to infusion of INT-1B3: low risk of infection, inflammation of the vein, blood clots of the catheter or vein, especially if an IV line has recently been inserted, or unintended leakage of medication to the surrounding tissues, which can cause swelling and / or pain.
- Signs of inflammation can occur: these include flu-like symptoms; low or high blood pressure with dizziness or fainting; hives (itchy stretch marks); feelings of fear; breathing problems; and liver infection / injury.
- Allergic reaction to INT-1B3: the most common reported side effects considered related to INT-1B3 are fatigue, constipation, skin rash, fever, inflammation of a vein, sometimes with a blood clot in the vein, and musculoskeletal events such as muscle pain, joints pain, muscle spasm, infusion related reaction (includes one or more of the symptoms: chills, fever, pain or cramps in muscles and joints, non-cardiac chest pain, headache, fever changes in blood pressure). Few patients experienced more severe medical events like acute kidney injury, increased blood bilirubin, fatigue, hypertension and a blood clot of the vein. None of these were life-threatening
- ECGs: The use of adhesive electrodes (ECG leads) may be accompanied by mild and temporary reddening and/or itching of the skin.
- CT/MRI scan: Participants will be exposed to radiation when undergoing a CT scan. The extra radiation falls within the limits set for this type of extra radiation exposure. For some CT/MRI scans it is necessary that participants are injected with a contrast agent. There is a small risk of developing an allergic reaction to the contrast agent. This reaction can be mild (itching, rash, nausea) or severe (difficulty breathing or state of shock). Most allergic reactions can be controlled with medication. The contrast agent can also cause dehydration or damage the kidneys, which at worst results in renal failure. If participants are dehydrated or have poor renal function, the study doctor can decide to take a blood sample to check the kidney function well enough, prior to making a CT/MRI scan. It is possible to feel claustrophobic in an MRI.
- ECHO/MUGA: Monitoring of the heart function can be done per standard care using echocardiography with no radiation exposure. The heart function can also be monitored with a multigated acquisition (MUGA) scan. For the MUGA scan, participants will receive a radioactive substance. The dose of radioactivity is very low, it is safe and does not give side effects. The body will get rid of it through your kidneys within about 24 hours.

# Contacts

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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

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

## Inclusion criteria

1. Patient provided a signed written informed consent before any screening procedure
2. Patient with (a) lesion(s) assessable for sequential biopsies (baseline and on treatment)
3. Patient is male or female, >=18 years of age (adult patients)
4. Patient with histologically or cytologically confirmed advanced and/or metastatic solid tumor, with progressive disease at baseline, for whom no standard treatment is available or who have declined standard therapy
5. Patient with evaluable disease per RECIST v1.1, iRECIST or mRECIST (for HCC patients)
6. Patient with a predicted life expectancy of * 12 weeks
7. Patient with Eastern Cooperative Oncology Group (ECOG) performance status of Grade 0 - 1
8. Patient with hemoglobin >= 9.0 g/dL, platelet count >= 75×109/L, and absolute neutrophil count >= 1.0×109/L
9. Patient with adequate renal function (creatinine level within normal institutional limit defined as CrCl (corrected for body surface area (BSA)) or calculated creatinine clearance >= 50 mL/min/1.73 m2 (CKD-EPI calculation, see

Appendix 11.1)
10. Patient with adequate liver function (aspartate transaminase and/or alanine transaminase <3 times institutional upper limit of normal (ULN) (or <= 5 times ULN for patients with liver metastases), total bilirubin <= 1.5 times ULN (or <= 3 x ULN for patients with Gilbert*s disease)
11. Patient with adequate coagulation tests: international normalized ratio or prothrombin time (PT) and activated partial thromboplastin time (aPTT) within 1.5 times ULN
12. Female patient of childbearing potential (defined as < 12 continuous months of amenorrhea with no identified cause other than menopause or not surgically sterile), must have a negative pregnancy test within 7 days before first administration of study medication and agree to use highly effective methods of contraception during the treatment until 60 days after the last administration of the study medication.
Examples of highly effective contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices. Hormonal contraceptive methods must be supplemented by a barrier method
The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptom-thermal, or post ovulation methods) and withdrawal are not acceptable methods of contraception
13. Male patients with a female partner of childbearing potential must agree to remain sexually abstinent or use adequate contraception (agreement to use a barrier method of contraception) during the treatment phase and 60 days after the last dose of the study medication. In addition, male patients must be willing to stop sperm donation during this time
14. Patient is able and willing to comply with the protocol and the restrictions and assessments therein.

Additional inclusion criteria for dose-expansion phase (Phase Ib):
15. Patient with measurable disease per RECIST v1.1, iRECIST or mRECIST (for HCC) and at least 1 (additional) lesion accessible for sequential biopsies (baseline and on-treatment)
16. Patient has advanced or metastatic HCC or TNBC with histological or cytological confirmation (histological confirmation can be obtained per screening biopsy for HCC)
17. Patient has previously received all systemic standard therapies with proven clinical benefit, and progressed or relapsed thereafter, or was ineligible for standard therapies in the judgment of the treating physician
a) Not more than one line of previous therapy with immune checkpoint inhibitor therapy either alone or in combination is allowed

## Exclusion criteria

1. Patient on any other anti-cancer therapy (cytotoxic, biologic or investigational agents), unless at least 4 weeks (or 5 half-lives, whichever is shorter, 6 weeks for mitomycin-C or nitrosoureas), have elapsed since the last dose before the first administration of INT-1B3 At least 2 weeks should have elapsed since receiving non-palliative radiotherapy. Chronic treatment with non-investigational gonadotropin-releasing hormone analogs or other hormonal or supportive care is permitted
2. Patient with known central nervous system (CNS) metastases, unless previously treated and well-controlled for at least 1 month (defined as clinically stable, no edema, no steroids and stable in 2 scans at least 4 weeks apart)
3. Patient with concomitant second malignancies unless curatively treated at least 2 years before study entry with no additional therapy required or anticipated to be required during the study period
4. Patient with major surgery within 5 weeks before initiating treatment or with minor surgical procedure within 7 days before initiating treatment (except for port-a-cath placement or biopsy)
5. Patient with active autoimmune disease or persistent immunemediated toxicity caused by immune checkpoint inhibitor therapy of grade >= 2 (patients with autoimmune-related hyperthyroidism, autoimmune-related hypothyroidism in remission, or with a stable dose of hormone-replacement, vitiligo, or psoriasis not requiring systemic therapy (>10mg prednisone equivalent) or controlled Type 1 diabetes mellitus, may be included)
6. Patient with toxicity (except for alopecia) related to prior anti-cancer therapy and/or surgery, unless the toxicity is either resolved, returned to baseline or Grade 1 (or are allowed according to other in/exclusion criteria)
7. Patient with any active neuropathy > Grade 2 (National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE] v5.0)
8. Patient with a history of life-threatening (Grade 4) toxicity related to prior immune therapy or severe (Grade 3) toxicity that resulted in permanent discontinuation after rechallenge with immune therapy
9. Patient with any condition requiring concurrent use of systemic immunosuppressants or corticosteroids at a daily dose > 10 mg prednisone equivalent or other immunosuppressive medications within 14 days of study medication administration (permitted: premedication for i.v. contrast, treatment with a short course of steroids (< 5 days) up to 7 days before initiating study medication, and topical glucocorticoids, or steroid replacement doses for adrenal or pituitary insufficiency)
10. Patient with evidence of active infection that requires systemic antibacterial, antiviral, or antifungal therapy <= 7 days before the first dose of study medication
11. Patient with uncontrolled or significant cardiovascular disease including, but not limited to, any of the following:
a) Left ventricular ejection fraction (LVEF) <= 50 % determined by

echocardiogram or multi-gated acquisition (MUGA) scan
b) High risk or uncontrolled clinically significant arrhythmias (such as atrial fibrillation and conduction disorders, ventricular tachycardia, ventricular fibrillation, or torsade de pointes)
c) Treatment with drugs that are generally considered to have a high risk of causing torsade de pointes (it will be at the discretion of the treating physician to discontinue or substitute as appropriate; if discontinued, the washout period needs to be at least 5 half-lives of the drug)
d) QT interval corrected using Fridericia*s formula (QTcF) prolongation > 480 msec
e) Cerebral vascular accident/stroke or myocardial infarction < 6 months prior to enrollment
f) Uncontrolled hypertension (systolic > 150 millimeter of mercury [mmHg] and/or diastolic > 100 mmHg)
g) Unstable angina within the past 6 months, congestive heart failure (CHF) defined as New York Heart Association (NYHA) class II -IV, hospitalization for CHF (any NYHA class) within 6 months before the start of trial treatment
h) Medical history of deep vein thrombosis or pulmonary embolism
12. Patient with active or chronic hepatitis B (positive for HBsAg or anti-HBsAg and anti-HBcAg antibodies) or C (positive for anti-HCV antibody or HCV RNA quantitation)
a) For the dose escalation phase, serology testing may be omitted at the investigator*s discretion if there are no clinical signs suggestive of hepatitis infections.
b) Subjects with positive HBV serology are eligible if quantitative PCR for plasma HBV-DNA is negative and the subject will be receiving prophylaxis for potential HBV reactivation.
c) Subjects with positive HCV serology are eligible if quantitative PCR for plasma HCV RNA is negative.
13. Patient with known history of presence of human immunodeficiency virus (HIV), patients are NOT required to be tested for the presence of HIV before therapy on this protocol)
14. Patient with any known or underlying medical, psychiatric condition, and/or social situations that, in the opinion of the investigator, would limit compliance with study requirements
15. Patient with history of allergy to the study medication or any of its excipients
16. Patient that received packed red blood cells or platelet transfusion within 2 weeks of the first dose of study medication
17. Female patient: pregnant or breastfeeding
18. Involvement in the planning and/or conduct of the study (applies to Sponsor staff, contract research organization (CRO) staff, and/or staff at study site)

# 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: | Pending |
| Start date (anticipated): | 18-02-2021 |
| Enrollment: | 40 |
| Type: | Anticipated |

# Ethics review

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|---|---|
| Approved WMO Date: | 06-01-2020 |
| Application type: | First submission |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 24-04-2020 |
| Application type: | First submission |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 14-05-2020 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 26-07-2021 |
| Application type: | Amendment |

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|---|---|
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 05-10-2021 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 21-10-2021 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 03-02-2022 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 12-04-2022 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 13-05-2022 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 07-06-2022 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 27-06-2022 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO | |

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|---|---|
| Date: | 16-08-2022 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 16-09-2022 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |

# 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 | EUCTR2019-004436-39-NL |
| CCMO | NL72232.000.19 |