A Phase 1, Open-Label, multicenter Study of INCA00186 as monotherapy or in combination with immunotherapy in participants with advanced solid tumors

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Miscellaneous and site unspecified neoplasms benign
Study type	Interventional

Summary

ID

NL-OMON53794

Source
ToetsingOnline

Brief title
INCA0186-101

Condition

- Miscellaneous and site unspecified neoplasms benign

Synonym
Advanced Solid Tumors

Research involving
Human

Sponsors and support

Primary sponsor: Incyte Corporation

Source(s) of monetary or material Support: de sponsor

Intervention

Keyword: advanced solid tumors, INCA00186, safety, tolerability

Outcome measures

Primary outcome

* Dose Limiting Toxicities

* Adverse Events (AEs), assessed by physical examinations, evaluating changes in vital signs and ECGs, and through clinical laboratory blood sample evaluations.

* Impact on study treatment, assessed by treatment interruptions, dose reductions, and withdrawal of study treatment due to AEs.

Secondary outcome

* PK parameters for INCA000186 including Cmax, tmax, Ctau, AUC, CL, Vz, and t* as deemed appropriate.

* Blockade of CD73 enzymatic activity.

* Objective response: CR or PR, as determined by investigator by radiographic disease assessment according to RECIST v1.1.

* Disease control: CR, PR, or SD as determined by investigator by radiographic disease assessment according to RECIST v1.1.

* Duration of response: time from earliest date of disease response (CR or PR) until earliest date of disease progression as determined by investigator by radiographic disease assessment according to RECIST v1.1, or death due to any cause, if occurring sooner than progression.

Study description

Background summary

The immune system plays an important role in cancer prevention, development, and defense. The evolution of immunotherapy has significantly changed the treatment landscape for multiple tumor types. Nevertheless, many cancer patients either do not respond or progress after an initial response to immune checkpoint therapy. Development of new treatment approaches to overcome immunosuppressive mechanisms within the tumor microenvironment therefore represents a high priority. INCA00186 is a humanized, Fc-silenced IgG1 mAb that binds to human CD73 and antagonizes
CD73 function. In addition, the antibody has been engineered to minimize Fc receptor engagement in order to avoid any potential immune mediated toxicity against CD73-expressing cells in nonmalignant tissue.

Study objective

The primary objective is to evaluate the safety, tolerability, and doselimiting toxicities, and determine the recommended dose for expansion
of INCA00186 as monotherapy and of combination treatments of INCA00186 with retifanlimab and/or INCB106385 in participants with
advanced solid tumors.
The secondary objectives are: To evaluate the pharmacokinetics of INCA00186 as monotherapy or in combination with retifanlimab and/or
INCB106385, to evaluate the intratumoral pharmacodynamic activity of INCA00186 as monotherapy and to determine the preliminary efficacy of
INCA00186 as monotherapy or in combination with retifanlimab and/or INCB106385 in terms of objective response rate (ORR), disease control
rate (DCR), and duration of response (DOR).

Study design

This is a multicenter, open-label, dose-escalation, and dose-expansion FIH, Phase 1 clinical study to investigate the safety, tolerability, PK profile, pharmacodynamics, and preliminary clinical efficacy of INCA00186 when given as monotherapy and in combination with retifanlimab and/or INCB106385 in participants with selected advanced solid tumors including SCCHN and specified GI malignancies.
Phase 1a will consist of a dose escalation for each treatment group using a hybrid design. This will allow evaluation of the safety and tolerability of the following study treatments in participants with advanced solid tumors (limited to CD8 T-cell-positive advanced SCCHN or specified GI malignancies [defined as CRC, gastric/GEJ cancer, HCC, PDAC, or SCAC] after initial dose escalation cohorts):

• INCA00186 as monotherapy (TGA)
• INCA00186 in combination with retifanlimab (TGB1)
• INCA00186 in combination with INCB106385 (TGB2)
• INCA00186 in combination with retifanlimab and INCB106385 (TGC)
At each dose level, only one participant will be treated first with a subsequent waiting period of * 24 hours to evaluate safety and tolerability, before treatment of the remaining participants at that dose level can start.
Following initial dose escalation cohorts in each of the treatment groups, in which participants with advanced solid tumors will be enrolled, the sponsor will restrict enrollment into the subsequent dose escalation cohorts to participants with CD8 T-cell-positive advanced SCCHN or specified GI malignancies (ie, the same inclusion criteria apply as for Phase 1b) and pre- and on-treatment biopsies will become mandatory. This may occur before opening enrollment into the second dose level or anytime thereafter and will be based on emerging PK data (ie, saturation of the TMDD).
This change in enrollment criteria and mandating biopsies will be clearly communicated to sites (through a memorandum).
Phase 1b is a dose expansion to better characterize the safety, tolerability, PK, pharmacodynamic effects, and preliminary tumor activity of INCA00186 as monotherapy or in combination with retifanlimab and/or INCB106385 at the RDE for the monotherapy and each of the combination
therapies in a total of approximately 120 evaluable participants. Participants in Phase 1b will be limited to those with selected CD8 T-cell-positive advanced or metastatic SCCHN or specified GI malignancies (defined as CRC, gastric/GEJ cancer, HCC, PDAC, or SCAC).
TGA (INCA00186 monotherapy)
* SCCHN: 10 participants
* Specified GI malignancies: 10 participants
TGB1 (INCA00186 + retifanlimab)
* SCCHN: 10 participants
* Specified GI malignancies: 10 participants
TGB2 (INCA00186 + INCB106385)
* SCCHN: 20 participants
* Specified GI malignancies: 20 participants
TGC (INCA00186 + retifanlimab + INCB106385)
* SCCHN: 20 participants
* Specified GI malignancies: 20 participants

Intervention

Phase 1a (dose increase) and phase 1b (dose extension):
• TGA: INCA00186 monotherapy (up to 2 years of treatment), with the option of adding treatment with retifanlimab or INCB106385
• TGB1: INCA00186 + retifanlimab (maximum 2 years of treatment), with the option of adding a treatment with INCB106385
• TGB2: INCA00186 + INCB106385 (maximum 2 years of treatment), with the option of adding treatment with retifanlimab

• TGC: INCA00186 + retifanlimab + INCB106385 (maximum 2 years of treatment)

Study burden and risks

By participating in the study, the participant helps study physicians gain more insight into the treatment of advanced malignancies. The risk of side effects is expected to be small in patients and will be carefully monitored. Therefore, the overall benefit-risk profile of this study remains favorable.

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

Participants are eligible to be included in the study only if all of the

following criteria apply:
1. Ability to comprehend and willingness to sign a written ICF for the study.
2. Male or female participant aged 18 years or older inclusive at the time of signing the ICF.
3. Must be willing and able to conform to and comply with all Protocol requirements, including all scheduled visits and Protocol procedures.
4. Willingness to undergo pre- and on-treatment tumor biopsy (core or excisional).
5. Have CD8 T-cell-positive tumors based on evaluation of CD8+ T-lymphocyte presence by IHC performed on pretreatment tumor biopsy tissue.
6. ECOG performance status 0 or 1.
7. Measurable disease according to RECIST v1.1.
8. Phase 1a early dose level cohorts in each of the treatment groups only: Participants with advanced or metastatic solid tumors experiencing disease progression after treatment with available therapies, including anti-PD-(L)1 therapy (if applicable), that are known to confer clinical benefit, or who are intolerant to, or ineligible for standard treatment. Prior anti-PD-(L)1 therapy should not have been discontinued because of intolerance.
9. Participants with SCCHN:
a. Participants with histologically or cytologically confirmed squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx not amenable to local therapy with curative intent (surgery or radiation with or without chemotherapy).
b. Participants should have disease progression after treatment with available therapies, including anti-PD-(L)1 therapy (alone or as part of a combination), that are known to confer clinical benefit or who are intolerant to or ineligible for standard treatment. Prior anti-PD-(L)1 therapy should not have been discontinued because of intolerance.
10. Participants with specified GI malignancies: Histologically or cytologically confirmed advanced or metastatic CRC, gastric/GEJ cancer, HCC, PDAC, or SCAC.
a. Participants should have disease progression after treatment with available therapies, including anti-PD-(L)1 therapy (if applicable), that are known to confer clinical benefit or who are intolerant to or ineligible for standard treatment. Prior anti-PD-(L)1 therapy should not have been discontinued because of intolerance.
11. For participants to be enrolled in cohorts including INCB106385: The ability to swallow oral medication.
12. Willingness to avoid pregnancy or fathering children based on the criteria below:
a. Male participants with reproductive potential must agree to take appropriate precautions to avoid fathering children (with at least 99% certainty) and refrain from donating sperm from screening through 190 days after the last dose of study treatment. Permitted methods that are at least 99% effective in preventing pregnancy should be communicated to the participants and their understanding confirmed.

b. Female participants who are WOCBP must have a negative pregnancy test at screening (serum test) and before the first dose of Day 1 (urine test) and must agree to take appropriate precautions to avoid pregnancy (with at least 99% certainty) and refrain from donating oocytes from screening through 190 days after the last dose of study treatment. Permitted methods that are at least 99% effective in preventing pregnancy should be communicated to the participants and their
understanding confirmed.
c. Female participants not considered to be of childbearing potential as defined are eligible.

Exclusion criteria

Participants are excluded from the study if any of the following criteria apply:
1. Clinically significant cardiac disease, unstable angina, acute myocardial infarction within 6 months of Cycle 1 Day 1, and New York Heart Association Class III or IV congestive heart failure.
2. History or presence of an ECG abnormality that, in the investigator's opinion, is clinically meaningful. For participants to be enrolled in cohorts including INCB106385, screening QTcF interval > 450 milliseconds (ms) is excluded; in the event that a single QTc is > 450 ms, the participant may enroll if the average QTc for the 3 ECGs is < 450 ms.
3. Known active CNS metastases and/or carcinomatous meningitis.
4. Participants who have active or inactive autoimmune disease or syndrome (eg, rheumatoid arthritis, moderate or severe psoriasis, multiple sclerosis, inflammatory bowel disease) that has required systemic treatment in the past 2 years or who are receiving systemic therapy for an autoimmune or inflammatory disease (ie, with use of disease modifying agents, corticosteroids, or immunosuppressive drugs).
5. Diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (doses > 10 mg daily of prednisone or equivalent) or any other form of immunosuppressive therapy within 7 days before the first dose of study treatment. Use of short courses of steroids for procedure
prophylaxis, inhaled or topical steroids, or systemic corticosteroids <= 10 mg/day is permitted.
6. Known additional malignancy that is progressing or requires active treatment, or history
of other malignancy within 2 years of the first dose of study treatment with the exception
of cured basal cell or squamous cell carcinoma of the skin, superficial bladder cancer,
prostate intraepithelial neoplasm, carcinoma in situ of the cervix, or other noninvasive or
indolent malignancy, or cancers from which the participant has been disease

free > 1 year after treatment with curative intent.
7. Participants with exclusionary laboratory values at screening (see protocol)
8. Has not recovered to <= Grade 1 from toxic effects of prior therapy (including prior immunotherapy) and/or complications from prior surgical intervention before starting study treatment.
9. Evidence of interstitial lung disease, history of interstitial lung disease, or active noninfectious pneumonitis.
10. Immune-related toxicity during prior immune therapy for which permanent discontinuation of therapy is recommended (per product label or consensus guidelines), OR any immune-related toxicity requiring intensive or prolonged immunosuppression to manage (with the exception of endocrinopathy that is well-controlled on replacement hormones).
11. Prior treatment with any adenosine pathway targeting drugs (eg, A2A receptor and/or A2B receptor antagonists, anti-CD38, anti-CD39, anti-CD-73/CD73 antagonists).
12. Any prior chemotherapy, biological therapy, or targeted therapy to treat the participant's disease within 5 half-lives or 28 days (whichever is shorter) before the first dose of study treatment.
13. Any prior radiation therapy within 28 days before the first dose of study treatment.
14. Undergoing treatment with another investigational medication or having been treated with an investigational medication within 5 halflives or 28 days (whichever is shorter) before the first dose of study treatment.
15. For participants to be enrolled in cohorts including INCB106385: concomitant treatment with strong CYP3A4 inhibitors or inducers.
16. Receipt of a live virus vaccine within 30 days of the first dose of study treatment.
17. Infection requiring parenteral antibiotics, antivirals, or antifungals within 1 week of the first dose of study treatment.
18. Known or suspected SARS-CoV-2 infection at the time of enrollment.
19. Active HBV or HCV infection that requires treatment. HBV-DNA and HCV-RNA must be undetectable. Participants who have cleared a prior HBV infection (defined as HBsAg negative, HBsAg antibody positive, and anti-HBc antibody positive) are eligible for the study.
20. Known history of HIV (HIV 1/2 antibodies).
21. History of organ transplant, including allogeneic stem-cell transplantation or CAR-T cell therapy.
22. Known hypersensitivity or severe reaction to any component of study drug(s) or formulation components.
23. For participants to be enrolled in cohorts including INCB106385: Inability to swallow food or any concomitant condition of the upper GI tract that precludes administration of oral medications.
24. Is pregnant or breastfeeding.
25. Any condition in the PIs judgment that will interfere with study participation.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-02-2023
Enrollment:	35
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	INCA00186
Generic name:	not available
Product type:	Medicine
Brand name:	INCB106385
Generic name:	not available
Product type:	Medicine
Brand name:	Retifanlimab
Generic name:	not available

Ethics review

Approved WMO Date:	21-04-2022
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	15-06-2022

Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	05-08-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-08-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-04-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-05-2023
Application type:	Amendment
Review commission:	METC NedMec

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	EUCTR2021-001263-24-NL
CCMO	NL79905.031.22