A Phase 1a/1b Study Exploring the Safety and Tolerability of INCB081776 in Participants With Advanced Malignancies

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This first-in-man study will investigate the safety and tolerability as well as establish a recommended dose of INCB081776 as a monotherapy (Part 1) and then in combination with INCMGA00012 (Part 2) in participants with advanced malignancies. During...

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

Summary

ID

NL-OMON52063

Source
ToetsingOnline

Brief title
INCB 81776-101

Condition

- Miscellaneous and site unspecified neoplasms benign

Synonym
advanced maligancies

Research involving
Human

Sponsors and support

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

Intervention

Keyword: advanced solid tumors, INCB081776, Safety, Tolerability

Outcome measures

Primary outcome

Frequency, duration, and severity of AEs and evaluation of DLTs through physical examinations, by evaluating changes in vital signs and ECGs, and through clinical laboratory blood and urine sample evaluations.

Identification of the RDE for INCB081776 alone or in combination with INCMGA00012

Secondary outcome

- Determination of PK of INCB081176 including Cmax, Tmax, Cmin, AUC0-t, C*, AUC*, t*, *z, CL/F, and Vz/F, which will be summarized.

- PK/pharmacodynamic correlation.

- Objective response, defined as the percentage of participants having CR or PR per RECIST v1.1.

- Disease control rate, defined as the percentage of participants having CR, PR, or SD per RECIST v1.1.

- Duration of response: defined as the time from earliest date of disease response until the earliest date of disease progression per RECIST v1.1 or death due to any cause, if occurring sooner than progression.

Study description

Background summary

Receptor tyrosine kinases, like AXL and MER, are cell surface proteins that transmit signals from the extracellular environment to the cell cytoplasm and nucleus to regulate cellular events such as survival, growth, proliferation, differentiation, adhesion, and migration. AXL contributes to several fundamental mechanisms of malignancy by promoting cancer cell migration and invasion, enhancing tumor angiogenesis, and facilitating cancer cell survival and tumor growth and also translocations of TMEM87B-MER and constitutive activation of MER have been identified in multiple malignancies, including triple negative breast cancer, lung cancer, ovarian cancer, bladder cancer, and cervical cancer. INCB081776 is an orally administered, potent, and selective inhibitor of AXL and MER kinases.

Study objective

This first-in-man study will investigate the safety and tolerability as well as establish a recommended dose of INCB081776 as a monotherapy (Part 1) and then in combination with INCMGA00012 (Part 2) in participants with advanced malignancies. During Part 1, the primary objective is to establish a safe and tolerable single-agent dose for further investigation. Following identification of tolerable dose(s) of single-agent INCB081776, participants with solid tumors will then be enrolled in Part 2 of the study to evaluate the safety and tolerability of INCB081776 in combination with INCMGA00012 and to establish recommended dose for expansion (RDE(s)) of INCB081776 in combination with INCMGA00012.

Study design

This is a Phase 1a/1b, open-label study to investigate both single-agent INCB081776 and INCB081776 in combination with INCMGA00012 in participants with advanced malignancies. The study consists of 2 parts.
Part 1: Single-Agent INCB081776
The study will begin with Part 1A. Initially, 3 participants at the starting dose level received a single dose of INCB081776 followed by a timed PK assessment to confirm exposure approximately 1 week before continuous administration is initiated. A dose-finding stage with single-agent INCB081776 using a 3 + 3 + 3 design will be performed to assess the safety and tolerability and to identify RDE(s) of INCB081776 in participants with advanced solid tumors. Upon selection of RDE(s) in Part 1A, Part 1B will be initiated. Part 1B will include 4 independent tumor-specific (melanoma, NSCLC, SCCHN, and soft-tissue sarcoma) dose expansion cohorts of approximately 12 participants each to further characterize the safety, tolerability, efficacy, and pharmacodynamic effects of the RDE(s) of INCB081776.
Part 2 will comprise Part 2A and Part 2B. Part 2A is a dose-finding stage, which will be performed using a 3 + 3 + 3 design to assess the safety and tolerability of INCB081776 in combination with INCMGA00012 in participants with advanced solid tumors.Part 2B is a dose expansion to further evaluate the

safety, tolerability, efficacy, and pharmacodynamic effects at the RDE(s) of INCB081776 in combination with INCMGA00012 determined in Part 2A.

Intervention

- Part 1: Single-agent INCB081776
- Part 2: Combination INCB081776 + INCMGA00012

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

1. Participant must be >= 18 years of age at the time of signing the ICF.
2. Participant (or legally acceptable representative if applicable) provides written informed consent for the study.
3. Must be willing and able to conform to and comply with all protocol requirements,
including, all scheduled visits, protocol procedures, and the ability to swallow oral capsules.
4. Part 1A, 1B, 2A, and 2B: Histologic or cytologic evidence of a solid neoplasm for
which no standard therapy is available, or have progressed despite standard therapy or are
intolerant to standard therapy, which may include chemotherapy, targeted therapy,
biological therapy, and immunotherapy, inclusive of the cohort-specific requirements
outlined below:
• Measurable lesions per RECIST v1.1 that are considered nonamenable to surgery or other curative treatments or procedures, with at least 1 target lesion available for evaluation. Tumor lesions located in a previously irradiated area or in an area subjected to other loco-regional therapy are considered measureable if progression has been demonstrated in the lesion.
• Part 1A and Part 2A only:
* Histologically confirmed advanced and/or metastatic solid tumors that are considered unresectable and may include but are not limited to the following tumor types: gastric or GEJ adenocarcinoma, HCC, melanoma, NSCLC, RCC, soft-tissue sarcoma, SCCHN (recurrent or metastatic), TNBC, or urothelial carcinoma. Additionally, MSI-H tumors are included in this part.
• Part 1B and 2B only:
* Cohort 1: advanced or metastatic melanoma
* Must have received available SOC, including but not limited to 1 prior PD-1/L1 containing regimen (either as a single agent or in combination), received at least 2 doses of the anti-PD-1/L1 agent, and experienced PD during or after treatment.
* Known BRAF status (V600e and V600k).
* Ocular melanoma is excluded.
* Cohort 2: advanced or metastatic NSCLC
* Must have received available SOC, including but not limited to 1 prior PD-1/L1 containing regimen (either as a single agent or in combination), received at least 2 doses of the anti-PD-1/L1 agent, and experienced PD during or after treatment.
* Participants with tumors harboring known driver mutations (EGFR, ALK, ROS1,

BRAF) who have previously been treated with appropriate targeted agents are allowed to enroll.
* Known PD-L1 expression status and/or TPS
* Cohort 3: recurrent or metastatic SCCHN
* Must have received available SOC, including but not limited to 1 prior PD-1/L1 containing regimen (either as a single agent or in combination), received at least 2 doses of the anti-PD-1/L1 agent, and experienced PD during or after treatment.
* Known PD-L1 expression status and/or TPS
* Carcinoma of the nasopharynx, thyroid, salivary gland, or nonsquamous histologies are excluded.
* Cohort 4: advanced or metastatic soft-tissue sarcoma
* Must have received available SOC
* Eligible subtypes include leiomyosarcoma, poorly differentiated/dedifferentiated liposarcoma, high-grade pleomorphic undifferentiated sarcoma/MFH, myxofibrosarcoma, malignant peripheral nerve sheath tumor, epithelioid sarcoma, clear cell sarcoma, synovial sarcoma, rhabdomyosarcoma, fibrosarcoma, and angiosarcoma
* Must not have received prior anti-PD-1/L1 targeted treatment.
5. Part 1B and Part 2B: All participants enrolled into Part 1B or Part 2B must be willing
to provide a fresh baseline tumor biopsy and an on-study biopsy between Cycle 2 Day 1
and Cycle 3 Day 1.
ECOG performance status score of 0 or 1.
6. Willingness to avoid pregnancy or fathering children

Exclusion criteria

1. Participants receiving potent inhibitors or inducers of CYP3A4.
2. Participants with macular degeneration, proliferative diabetic retinopathy or diabetic
retinopathy with macular edema, retinal vein occlusions, uveitis, central serous retinopathy, leukemic retinopathy, inherited retinal degenerations, known family history of inherited retinal degenerations, and participants at risk for angle closure glaucoma from pupillary dilation are ineligible.
Participants with other clinically significant abnormalities identified during ophthalmic screening examinations that may confound ocular monitoring are ineligible.
3. Clinically significant cardiac disease, including LVEF<40%, unstable angina, acute
myocardial infarction within 6 months of Cycle 1 Day 1, New York Heart Association
Class III or IV congestive heart failure, and arrhythmia requiring therapy.
4. History or presence of an abnormal rhythm or pattern on ECG that, in the

investigator's
opinion would have a clinically meaningful impact on the study.
5. Untreated brain or CNS metastases or brain or CNS metastases that have progressed.
6. Participants who have active or inactive autoimmune disease or syndrome either
independent of prior therapy or induced by prior immune checkpoint inhibitor therapy that has required systemic treatment in the past 2 years or who are receiving systemic therapy for an autoimmune or inflammatory disease
7. Parts 1B, 2A, and 2B only: Participants with prior Grade 3 or higher immune-related
AEs or any ocular toxicity on prior immunotherapy.
8. Laboratory values not within the Protocol-defined range.
9. Participants receiving any vitamin K antagonists,
10. Treatment with anticancer medications or investigational drugs within the following
intervals before the first administration of study drug:
a. At least 14 days for chemotherapy, targeted small molecule therapy, or radiation
therapy. Participant must not have had radiation pneumonitis as a result of treatment.
b. At least 28 days for a prior monoclonal antibody used for anticancer therapy.
11. Has not recovered to <= Grade 1 or baseline from toxic effects of prior therapy (including
prior immunotherapy) and/or complications from prior surgical intervention.
12. Parts 1B, 2A, and 2B only: No use of systemic corticosteroids within 7 days before the
first dose of study treatment.
13. Receipt of a live vaccine within 3 months of the first dose of study treatment
14. Active infection requiring systemic therapy.
15. Evidence of HBV or HCV infection or risk of reactivation.
16. Known history of HIV (HIV 1/2 antibodies).
17. Known hypersensitivity or severe reaction to any component of study drugs or formulation components.
18. Is pregnant or breastfeeding or expecting to conceive or father children within the
projected duration of the study, starting with the screening visit through 190 days after
the last dose of study treatment.
19. Any condition that would, in the investigator's judgment, interfere with full participation
in the study, including administration of study treatment and attending required study
visits; pose a significant risk to the participant; or interfere with interpretation of study

data.
20. Inability of the participant to comprehend the ICF or unwillingness to sign the ICF.
21. Participants with known dysphagia, short-gut syndrome, gastroparesis, or other
conditions that limit the ingestion or gastrointestinal absorption of drugs administered
orally.
22. Evidence of interstitial lung disease, history of interstitial lung disease, or active,
noninfectious pneumonitis.
23. History of organ transplant, including allogeneic stem cell transplantation (except
Cohort 1C).
24. Diagnosis of oculocutaneous albinism.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	04-10-2022
Enrollment:	35
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	INCB081776
Generic name:	not available
Product type:	Medicine
Brand name:	Retifanlimab

Generic name:	Retifanlimab

Ethics review

Approved WMO Date:	14-04-2022
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-08-2022
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-09-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-10-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-05-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-08-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-05-2024
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-06-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2020-004867-26-NL
ClinicalTrials.gov	NCT03522142
CCMO	NL78217.078.22