# A Phase 1, Open-Label, Multicenter Study of INCB123667 as Monotherapy in Participants With Selected Advanced Solid Tumors

Published: 19-04-2022
Last updated: 05-10-2024

This study has been transitioned to CTIS with ID 2024-512822-28-00 check the CTIS register for the current data. The primary objective of this study is to evaluate the safety and tolerability and determine the MTD and RDE(s) of INCB123667 as...

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

## Summary

### ID

NL-OMON53884

**Source**
ToetsingOnline

**Brief title**
INCB 123667-101

### Condition

- Miscellaneous and site unspecified neoplasms benign

**Synonym**
Selected Advanced Solid Tumors

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Incyte Corporation

**Source(s) of monetary or material Support:** Incyte Corporation

## Intervention

**Keyword:** advanced solid tumors, INCB123667, safety, tolerability

## Outcome measures

### Primary outcome

• Occurrence of DLTs.

• Incidence of TEAEs, assessed by physical examinations, evaluating changes in vital signs and ECGs, and through clinical laboratory blood sample evaluations, collecting vital signs; and collecting laboratory data for hematology, serum chemistry, and urinalysis.

• Incidence of TEAEs leading to study drug treatment interruptions, dose reductions, and discontinuation of study drug due to AEs.

### Secondary outcome

* PK parameters for INCB123667, including Cmax, tmax, Ctau, AUC, CL (or CL/F), Vz (or Vz/F), and t* as deemed appropriate

* Objective response: defined as having a best overall response of CR or PR, as determined by the investigator by radiographic disease assessment according to RECIST v1.1.

* DCR: defined as having a best overall response of CR, PR, or SD as determined by the investigator by radiographic disease assessment according to RECIST v1.1.

* DOR: defined as the time from earliest date of disease response (CR or PR) until earliest date of disease progression as determined by the 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

Cyclin-dependent kinases are a family of serine/threonine kinases that, when bound to regulatory subunits known as cyclins, become fully activated and regulate various key cellular processes. CDKs are commonly grouped into 2 categories: CDKs that directly promote cell cycle progression, including CDK1, 2, 4, and 6, and CDKs that regulate gene transcription, such as CDK7 and CDK9. CDK1/cyclin B, CDK2/cyclin E, CDK4/cyclin D,
and CDK6/cyclin D are essential regulators in controlling cell cycle progression. The CDK2 pathway can influence tumorigenesis through multiple mechanisms, including cell cycle regulation via upregulation of CCNE; the regulatory cyclin for CDK2 and inactivation of CDK2 endogenous inhibitors, such as p27, that bind to CDK2/cyclin E complex and repress its activity, respectively; cell differentiation; cell senescence ; and cell apoptosis. Targeting CDK2 may be efficacious in a wide range of human cancers that have alterations activating CDK2 due to cyclin E1 overexpression or CCNE1 amplification. INCB123667 is a selective inhibitor of CDK2 and is proposed for the treatment of advanced or metastatic malignancies.

### Study objective

This study has been transitioned to CTIS with ID 2024-512822-28-00 check the CTIS register for the current data.

The primary objective of this study is to evaluate the safety and tolerability and determine the MTD and RDE(s) of INCB123667 as monotherapy in participants with selected advanced or metastatic solid tumors.
The secondary objective is to evaluate the PK of INCB123667 as monotherapy in participants with selected advanced or metastatic solid tumors and to determine the preliminary efficacy of INCB123667 as monotherapy in terms of ORR, DCR, and DOR in participants with selected advanced or metastatic solid tumors.

### Study design

This is a Phase 1, open-label, multicenter, dose-escalation, and dose-expansion clinical study to investigate the safety, tolerability, PK, pharmacodynamics, and preliminary efficacy of INCB123667 when given as monotherapy in participants with selected advanced or metastatic solid tumors.
Part 1a will consist of dose escalation using a statistical hybrid design, and the starting dose of INCB123667 will be 50 mg QD administered in 28-day

continuous treatment cycles. At each dose level, 1 participant will be observed for * 24 hours after administration of study drug and before subsequent participants begin study drug treatment. No more than 2 participants per dose level will begin study drug treatment within a 24-hour period.
Part 1b will consist of dose expansion to better characterize the safety, tolerability, PK, pharmacodynamics, and preliminary antitumor activity of INCB123667 as monotherapy administered at the RDE(s) defined in Part 1a in a total of approximately 210 participants. In the event more than 1 RDE is used within a particular disease group, participants will be randomly assigned to the RDE(s) within the selected disease group. Participants in Part 1b will be limited to those with documented CCNE1 amplification (as determined by a qualified local laboratory) or with cyclin E1 overexpression (as determined centrally by a sponsor's central laboratory using a CLIA assay) and with gynecologic tumors (Disease Groups 1 and 2: epithelial ovarian/fallopian/primary peritoneal carcinoma or clear cell ovarian cancer, or endometrial adenocarcinoma, uterine carcinosarcoma, or uterine papillary serous carcinoma), gastrointestinal tumors (Disease Group 3: gastric, GEJ, and esophageal adenocarcinomas), breast cancer (Disease Groups 4and 5: participants with TNBC or with HR-positive/HER2-negative breast cancer who have had disease progression on or been intolerant of a CDK4/6 inhibitor), or other tumor indications in participants who have had disease progression on prior standard treatment or are intolerant to or ineligible for standard treatment or there is no available treatment/therapy to improve the participant's disease outcome (Disease Group 6). For participants in Part 1b who are enrolled based on local documentation of CCNE1 amplification, confirmatory testing through the sponsor's central laboratory will be performed after enrollment.

### Intervention

Single agent INCB123667

### Study burden and risks

By participating in the study, participants will help researchers gain more insight into the treatment of advanced or metastatic solid tumors.
The risk of side effects is expected to be small (or reversible) in patients and will be carefully monitored. Given the severity of the disease, the overall benefit-risk profile of this study remains favorable.

## Contacts

**Public**
Incyte Corporation

Augustine Cut-Off 1801
Wilmington DE 19803
US
**Scientific**
Incyte Corporation

Augustine Cut-Off 1801
Wilmington DE 19803
US

# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

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

## Inclusion criteria

1. Ability to comprehend and willingness to sign a written ICF for the study.
2. Adults age 18 years or older at the time of signing the ICF. In France, adult (age of at least 18 and up to 99 years) male or female participants.
3. Willing and able to conform to and comply with all Protocol requirements, including all scheduled visits and Protocol procedures.
4. Life expectancy greater than 12 weeks.
5. ECOG performance status score of 0 or 1.
6. Disease progression on prior standard treatment, intolerance to or ineligibility for standard treatment, or no available treatment to improve the disease outcome.
7. Availability of a baseline archival tumor specimen or willingness to undergo a pretreatment and an on-treatment tumor biopsy (core or excisional) as applicable to obtain the specimen.
Note:
• For participants in Part 1a and Part 1b: Fresh pretreatment biopsy (within the screening/prescreening period) or archival tissue (collected within 2 years prior to C1D1) is required as described in the protocol and in the Laboratory Manual.

• For participants in Part 1b only: At least 5 participants per disease group will be required to provide an on-treatment tumor biopsy during the third/fourth week of study drug treatment (to obtain paired biopsies).
8. Diagnoses as follows:
a. For participants in Part 1a (dose escalation): Histologically or cytologically confirmed advanced or metastatic solid tumors. Documented CCNE1 amplification from a qualified local laboratory test is preferred but not mandatory.
b. For participants in Part 1b (dose expansion): Tumor tissue with CCNE1 amplification as determined by a qualified local laboratory or central confirmation of cyclin E1 overexpression as follows (this does not apply to participants in disease group 5):
* Participants with documentation of CCNE1 amplification obtained from a qualified local laboratory will be enrolled without central cyclin E1 overexpression prescreening but are still required to provide a tumor tissue sample (fresh sample or archival tissue) for retrospective central cyclin E1 overexpression evaluation.
* Participants without documentation of CCNE1 amplification obtained from a qualified local laboratory will provide a tumor tissue sample (a fresh sample if archival tissue within 2 years prior to C1D1 is not available) for prospective central cyclin E1 overexpression evaluation as part of eligibility prescreening. Only participants with cyclin E1 overexpression confirmed at a central laboratory using a CLIA assay will be allowed to enter the study. These participants will be required to sign a specific prescreening consent form before the prescreening tumor tissue is obtained; however, no other protocol assessments will be performed under the prescreening consent.

and with any of the following histologically or cytologically confirmed indications:
- Gynecologic malignancies
o Disease Group 1 (ovarian/fallopian/primary peritoneal cancer): Participants with advanced platinum-based chemotherapy-refractory or - resistant epithelial ovarian/fallopian/primary peritoneal carcinoma or clear cell ovarian cancer who have received up to 4 prior lines of systemic therapy administered for advanced or metastatic disease
or
o Disease Group 2 (endometrial/uterine cancer): Participants with advanced endometrial adenocarcinoma, uterine carcinosarcoma, or uterine papillary serous carcinoma who have received up to 3 prior lines of systemic therapy administered for advanced or metastatic disease.
Note (applicable to both Disease Groups 1 and 2): Maintenance treatment with bevacizumab or a poly (ADP-ribose) polymerase inhibitor following response to chemotherapy will not be counted as a separate line of therapy. Unlimited prior lines of endocrine therapy are allowed.

* Gastrointestinal malignancies
o Disease Group 3 (gastric, GEJ, and esophageal adenocarcinomas): Participants

with advanced gastric, GEJ, or esophageal adenocarcinomas who have received up to 3 prior lines of systemic therapy administered for advanced or metastatic disease

* Breast Cancer
o Disease Group 4 (TNBC): Participants with locally recurrent/advanced or metastatic TNBC who have received up to 2 prior lines of chemotherapy administered for advanced or metastatic disease.
o Disease Group 5 (HR-positive/HER2-negative breast cancer after progression or intolerant to a CDK4/6 inhibitor treatment): Participants with advanced HR-positive/HER2-negative breast cancer who have had disease progression on or been intolerant of a CDK4/6 inhibitor (HR+/HER2* defined as ER >1% and HER2 analysis will be conducted as per American Society of Clinical Oncology/College of American Pathologists guidelines [Wolff et al 2018]).These participants do not need to have documentation of CCNE1 amplification before enrollment in the study.
* Other tumor indications
o Disease Group 6 (other tumor indications): Participants with advanced solid tumors who have had disease progression on standard systemic therapies and received up to 4 prior lines of systemic therapy administered for advanced or metastatic disease

9. Measurable lesions by CT or MRI based on RECIST v1.1 criteria that are considered nonamenable to surgery or other curative treatments or procedures.
Note: Locally advanced disease must not be amenable to resection with curative intent or other curative treatments or procedures.
Note: Tumor lesions that are located in a previously irradiated area or in an area subjected to other locoregional therapy should only be selected as target lesions if progression has been demonstrated in such lesions.
Note: It is recommended that tumor lesions selected for biopsy not be selected as target lesions.

10. Ability to swallow and retain oral medication.

## Exclusion criteria

1. History of clinically significant or uncontrolled cardiac disease, including recent (within the last 12 months) unstable angina pectoris or acute myocardial infarction, or New York Heart Association Class III or IV cardiac disease, including preexisting clinically significant ventricular arrhythmia, congestive heart failure, cardiomyopathy not controlled by medication, or other clinically significant heart disease (ie, >= uncontrolled Grade 3 hypertension). Participants with a pacemaker and well-controlled rhythm for at least 1 month before the first dose of study drug will be allowed.
2. History or presence of an ECG abnormality that, in the investigator's

opinion, is clinically meaningful. Screening QTcF interval >450 milliseconds is excluded; in the event that a single QTc is >450 milliseconds, the participant may enroll if the average QTc for the 3 ECGs is <450 milliseconds.
3. Presence of chronic or current active infectious disease requiring systemic antibiotic, antifungal, or antiviral treatment. Participants with acute infection requiring antibiotic, antifungal, or antiviral treatment should delay screening/enrollment until the course of antibiotic, antifungal, or antiviral therapy has been completed and the infection is no longer active.
4. Untreated brain or CNS metastases or brain or CNS metastases that have progressed (eg, evidence of new or enlarging brain metastasis or new neurological symptoms attributable to brain or CNS metastases).
Note: Participants who have previously treated and clinically stable brain or CNS metastases (without evidence of progression by imaging for at least 4 weeks before the first dose of study drug and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastasis or CNS edema, and have not required steroids for at least 7 days before study drug are eligible.
5. Known additional malignancy that is progressing or requires active treatment, or history of other malignancy within 2 years of the first dose of study drug 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 for >1 year after treatment with curative intent.
6. Participants with laboratory values at screening defined in the protocol.
7. Significant concurrent, uncontrolled medical condition, including but not limited to the following:
a. Hepatic
* Known history of drug-induced liver injury; alcoholic liver disease; nonalcoholic steatohepatitis; primary biliary cirrhosis; ongoing extrahepatic obstruction caused by stones, cirrhosis of the liver, or portal hypertension.
b. Gastrointestinal
* Significant gastrointestinal disorder that could interfere with absorption, metabolism, or excretion of study drug, including gastrectomy, partial gastrectomy, or presence of a venting gastric tube that may interfere with absorption of the study drug.
* Recent (<= 3 months) history or ongoing partial or complete bowel obstruction, unless corrected by surgery.
* Any concomitant condition of the upper gastrointestinal tract that precludes administration of oral medications.
8. Has not recovered to <= Grade 1 from toxic effects of prior therapy and/or complications from prior surgical intervention before starting study drug.
Note: Participants with stable chronic conditions (<= Grade 2) not expected to resolve (such as neuropathy, hypothyroidism, and alopecia) are exceptions and may enroll.
9. Prior treatment with any CDK2 inhibitor.
10. Any change in endocrine therapy within 5 half-lives or 28 days (whichever

is shorter) before the first dose of study drug or any administration of targeted therapy, antibody, or hypomethylating agent to treat the participant's disease within 5 half-lives or 28 days (whichever is shorter) before the first dose of study drug.

# 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: | Recruiting |
| Start date (anticipated): | 27-10-2022 |
| Enrollment: | 15 |
| Type: | Actual |

## Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | INCB123667 |
| Generic name: | not available |

# Ethics review

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| Approved WMO Date: | 19-04-2022 |
| Application type: | First submission |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 08-07-2022 |

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| Application type: | First submission |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 29-07-2022 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 19-08-2022 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 21-02-2023 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 11-04-2023 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 11-12-2023 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 26-02-2024 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 26-03-2024 |
| 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 |
|---|---|
| EU-CTR | CTIS2024-512822-28-00 |
| EudraCT | EUCTR2021-005357-91-NL |
| ClinicalTrials.gov | NCT05238922 |
| CCMO | NL80935.078.22 |