A Phase 1/2, Open-Label, Dose-Escalation/Dose-Expansion, Safety and Tolerability Study of INCB059872 in Subjects With Advanced Malignancies

Published: 09-08-2017
Last updated: 12-04-2024

Primary objectives:* Part 1: To evaluate the safety and tolerability and determine the recommended dose(s) of INCB059872 for further study in advancedmalignancies.* Part 2: To further evaluate the safety and tolerability of INCB059872 for further...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON48925

Source
ToetsingOnline

Brief title
A Safety and Tolerability Study for patients with Advanced Malignancies

Condition

- Leukaemias
- Miscellaneous and site unspecified neoplasms malignant and unspecified
- Respiratory tract neoplasms

Synonym
advanced malignaties, several types of severe cancer

Research involving
Human

Sponsors and support

Primary sponsor: Incyte Biosciences UK Ltd
Source(s) of monetary or material Support: industry

Intervention

Keyword: Advanced Malignancies, Dose-escalation/dose-expansion, Lysine-specific demethylase 1 (LSD1) inhibitor, Phase1/2

Outcome measures

Primary outcome

* Parts 1 and 2: Safety and tolerability as assessed by monitoring frequency, duration, and severity of adverse events (AEs) through physical examinations, by evaluating changes in vital signs and electrocardiograms (ECGs), and through clinical laboratory blood and urine sample evaluations.

* Parts 3 and 4: Safety and tolerability as assessed by monitoring frequency, duration, and severity of AEs through physical examinations, by evaluating changes in vital signs and ECGs, and through clinical laboratory blood and urine sample evaluations in combinations therapies.

Secondary outcome

* Parts 1 and 2: Tumor response rates in those subjects with measurable disease or spleen volume changes as determined by investigator assessment of response per disease-specific guidelines.

* Solid tumors: Objective response rate (ORR), defined as the percentage of subjects having complete response (CR) or partial response (PR) will be determined by the investigator assessment of radiographic disease assessments per RECIST v1.1.

* Acute myeloid leukemia (AML)/myelodysplastic syndrome (MDS): ORR, defined as

the proportion of subjects who achieve CR or complete remission with incomplete hematologic recovery (CRi) per the International Working Group Response Criteria for Acute Myeloid Leukemia or the International Working Group Response Criteria for MDS, as applicable.

* MF: Change and percentage change in spleen volume reduction (SVR) as measured by magnetic resonance imaging (MRI; computed tomography [CT] scan in subjects who are not a candidate for MRI or when MRI is not readily available) at Week 12 when compared with baseline.

* Parts 3 and 4: Tumor response rates in those subjects with measurable disease as determined by investigator assessment of response per disease-specific guidelines.

* Small cell lung cancer (SCLC): ORR, defined as the percentage of subjects having CR or PR will be determined by the investigator assessment of radiographic disease assessments per RECIST v1.1.

* AML/MDS: ORR, defined as the proportion of subjects who achieve CR or CRi per the International Working Group Response Criteria for Acute Myeloid Leukemia or the International Working Group Response Criteria for MDS, as applicable.

* PK parameters of INCB059872 in plasma: Cmax, Tmax, Cmin, AUC0-t, t*, and Cl/F.

Exploratory Endpoints:

* Parts 1 and 2:

* Efficacy measured by

* Solid tumor, AML, and MDS: Duration of response, progression-free survival, and overall survival.

* MF: Change and percentage change in spleen volume reduction (SVR) as measured by MRI (CT scan in subjects who are not a candidate for MRI or when MRI is not readily available) at Week 24 when compared with baseline.

* Parts 3 and 4:

* Efficacy measured by duration of response, progression-free survival, and overall survival in SCLC and AML subjects.

* Assessment of the baseline level and changes in biomarkers and their correlation to INCB059872 treatment, including the following:

* Peripheral blood cell population or expression profile.

* Circulating proteins associated with differentiation, inflammation, immunity, metabolism, or tumor presence.

* Assessment of biomarkers in tumor tissues to predict the response to INCB059872 treatment.

* MF: Symptom burden in subjects with MF as assessed using the modified Myeloproliferative Neoplasm-Symptom Assessment Form diary and Patient Global Impression of Change.

Study description

Background summary

INCB059872 is a covalent flaven adenine dinucleotide (FAD)-directed inhibitor of lysinespecific demethylase 1 (LSD1) that is proposed for the treatment of advance malignancies. LSD1 regulates gene expression epigenetically by removing methylation marks from lysine 4 or
9 of histone H3. Target genes of LSD1 are involved in may biological processes, including cell growth, survival, differentiation, and stem cell homeostasis. Studies have shown that deregulated LSD1 activity is associated with human diseases, including cancer, where overexpression of LSD1 is frequently

associated with poor clinical outcomes.

Lysine Demethylase 1 Inhibitor in Oncology
Epigenetic modifications significantly contribute to the development of various cancers (Dawson and Kouzarides 2012). Analyses of cancer genomes have revealed that multiple epigenetic regulatory genes are often overexpressed or mutated in a variety of cancers (Shen and Laird 2013). One particular epigenetic enzyme that is associated with human cancer is LSD1, the first discovered histone demethylase and a key epigenetic regulator of chromatin architecture (Shi et al 2004). Methylated histone marks on H3K4 and H3K9 are coupled with transcriptional activation and repression, respectively. As part of the corepressor complex (eg, as corepressor of RE1 silencing transcription factor) (Stavropoulos et al 2006), LSD1 has been
reported to demethylate H3K4 and represses transcription, whereas LSD1 in the nuclear hormone receptor complex (eg, androgen receptor) may demethylate H3K9 to activate gene expression (Metzger et al 2005). This suggests that the substrate specificity of LSD1 can be
determined by associated factors, thereby regulating alternative gene expression in a contextdependent
manner. In addition to histone proteins, LSD1 demethylates several nonhistone proteins critical in the regulation of cell growth, differentiation, and survival pathways. These include p53 (Huang et al 2007), E2F (Kontaki and Talianidis 2010), STAT3 (Yang et al 2010), Tat (Sakane et al 2011), and myosin phosphatase target subunit 1 (Cho et al 2011). These findings suggest the potential for additional oncogenic roles of LSD1 beyond its epigenetic role in regulating chromatin remodeling. LSD1 also associates with other epigenetic regulators, such as DNA methyltransferase 1 (DNMT1) (Wang et al 2009) and histone deacetylase (HDAC) (You et al 2001). These associations augment the activities of DNMT or HDACs. LSD1 inhibitors may therefore potentiate the effects of HDAC or DNMT inhibitors (Han et al 2013, Singh et al 2011). LSD1 contributes to a variety of biological processes, including the regulation of cell proliferation, the epithelial-mesenchymal transition, cellular transformation of somatic cells, and self-renewal and differentiation, the latter impacting stem cell biology both in embryonic stem cells and in cancer stem cells (Chen et al 2012 , Adamo et al 2011). These cancer stem cells may render cancer cells resistant to conventional therapies, such as chemotherapy or radiotherapy, and promote tumor recurrence after treatment (Beck and Blanpain 2013). In this regard, LSD1 functions in maintaining an undifferentiated tumor initiating or cancer stem cell phenotype in a spectrum of cancers (Wang et al 2011, Zhang et al 2013). Notably, acute myeloid leukemia (AML) cells retain a less differentiated stem cell*like phenotype or leukemia stem cell (LSC) potential. Genome-wide gene expression analyses have revealed that LSD1 regulates a subset of genes involved in multiple oncogenic programs to maintain the LSC phenotype in AML, and inhibition of LSD1 has demonstrated therapeutic benefit in preclinical models of murine and human AML (Harris et al 2012, Schenk et al 2012). A variety of additional hematologic cancers also overexpress LSD1, including significant subsets of high-grade B-cell and T-cell

non- Hodgkin's lymphomas and Hodgkin's lymphomas (Niebel et al 2014), although the therapeutic benefit of LSD1 inhibition in these cancers has not yet been evaluated.
In addition to hematologic malignancies, overexpression of LSD1 is frequently observed in many types of solid tumors, and its expression is associated with a more clinically aggressive phenotype and poor prognostic outcome. Cancers in which overexpression of LSD1 has been documented include bladder cancer (Hayami et al 2011), small cell lung cancer (SCLC) (Mohammad et al 2015), non-SCLC (Lv et al 2012), breast cancer (Lim et al 2010), ovarian cancer (Konovalov and Garcia-Bassets 2013), glioma (Sareddy et al 2013), colorectal cancer (Hayami et al 2011, Ding et al 2013), a variety of sarcomas (Bennani-Baiti et al 2012), neuroblastoma (Schulte et al 2009), prostate cancer (Suikki et al 2010), esophageal squamous cell cancer (Yu et al 2013), papillary thyroid cancer (Kong et al 2013), and Ewing sarcoma (Sankar et al 2014). In these studies, either genetic knockdown of LSD1 expression or treatment with small-molecule inhibitors of LSD1 resulted in decreased cancer cell proliferation and/or induction of apoptosis both in vitro and in vivo. These findings suggest a potential therapeutic benefit of LSD1 inhibitors in a broad range of cancers beyond AML.

Study Rationale
Cancer has several common characteristic that can be observed across numerous tumor types.
One common characteristic is the uncontrolled growth and survival of cells and their ability to become invasive throughout the body. LSD1 contributes to tumor development by altering epigenetic marks on histones and nonhistone proteins. Accumulating data have validated that either genetic depletion or pharmacological inhibition of LSD1 normalizes oncogenic and cancer stem cell*like patterns of gene expression, thereby inducing differentiation programs, decreasing cell proliferation, and promoting apoptosis in cancer cells (Harris et al 2012, Schenk et al 2012). Therefore, LSD1 inhibitors have the potential to be effective treatments for human cancers with aberrant LSD1 activation.

Study objective

Primary objectives:

* Part 1: To evaluate the safety and tolerability and determine the recommended dose(s) of INCB059872 for further study in advanced malignancies.
* Part 2: To further evaluate the safety and tolerability of INCB059872 for further study in advanced malignancies.
* Part 3: To evaluate the safety and tolerability and determine the recommended dose of INCB059872 in combination with other therapies for further study in advanced malignancies.
* Part 4: To further evaluate the safety and tolerability of INCB059872 in

combination with other therapies in advanced malignancies.

Secondary objectives:

* Parts 1 and 2: To assess preliminary antitumor activity of INCB059872 as a monotherapy in subjects with advanced malignancies.
* Parts 3 and 4: To assess preliminary antitumor activity of INCB059872 in combination with other therapies in subjects with advanced malignancies.
* To evaluate the pharmacokinetics (PK) of INCB059872 and assess the effect of food (Treatment Group [TG] B1 only) on the PK of INCB059872.

Exploratory Objectives:
* Parts 1 and 2: To further evaluate the efficacy of INCB059872 as a monotherapy in subjects with advanced malignancies.
* Parts 3 and 4: To further evaluate the efficacy of INCB059872 in combination with other therapies in subjects with advanced malignancies.
* To assess the pharmacodynamics (PD) of INCB059872 and characterize the impact on biomarkers in peripheral blood and tumor tissue.
* To explore potential predictive biomarkers to identify subgroups that would benefit most from INCB059872.
* To evaluate preliminary efficacy of INCB059872 with respect to myelofibrosis (MF) symptoms.

Study design

This is an open-label, dose-escalation/dose-expansion study of the lysine-specific demethylase 1 (LSD1) inhibitor INCB059872 as a monotherapy and combination therapy in subjects with advanced malignancies. Subjects will receive INCB059872 doses once every other day (QOD) on a 28-day continuous therapy schedule; if QOD is well-tolerated, the next dose may be administered at a different dosing regimen (ie, once daily [QD]) but will not exceed the 100% dose escalation for a total daily dose. The study will be conducted in 4 parts: Parts 1 and 2 will evaluate INCB059872 as monotherapy, with Part 1 for dose escalation and Part 2 for dose expansion, and Parts 3 and 4 will evaluate INCB059872 in combination with select therapies, with Part 3 for combination dose escalation and Part 4 for combination dose expansion. Part 1 (monotherapy dose escalation) will determine the starting dose(s) of INCB059872 for dose expansion, based on maximum tolerated dose (MTD). The recommended dose(s) will be taken forward into Part 2 (monotherapy dose expansion). It is important to note that there may be a different MTD in different treatment groups. The initiation of Part 2 will be based on further review of the ongoing clinical study and preclinical data of INCB059872 and information from literature. Part 3 (dose escalation of INCB059872 in combination therapy) will be initiated after the MTD in Part 1 is determined. Part 4 (dose expansion of INCB059872 in combination therapy) will explore the dose(s) confirmed in Part 3 and the

dose(s) may be different based on combination therapy and/or tumor type.

Intervention

INCB059872 will be self-administered orally QOD on a 28-day cycle. In each cycle of the QOD dosing schedule, subjects should receive 14 doses of INCB059872. Tablets will be available in 1 mg strength. The initial starting dose for Part 1 will be 2 mg. For QOD administration, if a dose is missed by more than 24 hours, the subject should skip the dose and take the next scheduled dose at the usual time. INCB059872 tablet should be taken on an empty stomach if possible (refrain from food consumption during the period 2 hours before and 1 hour after taking INCB059872). For subjects participating in the food-effect portion of the study in Part 2, Expansion Cohort B1, a high-fat, high-calorie meal will be consumed within 30 minutes before taking INCB059872 on Cycle 2 Day 1. Alternative dosing regimens (ie, once daily) may be explored based on emerging PK/PD and safety
data.

Study burden and risks

Additional visits to the hospital, having additional physical tests including hepatitis blood test. Additional imaging and biopsies.
Possible side effects from blood draws or biopsies are fainting, bruising, soreness, and tenderness at the needle site and on rare occasions, infection. Rash or minor irritation of the skin from ECG pads. Risks of bone marrow biopsy include pain, redness, swelling, bruising, excessive bleeding, particularly in people with low platelets, infection, especially in people with weakened immune systems, long-lasting discomfort at the biopsy site and, if breastbone is chosen as the biopsy site, penetration of the breastbone (sternum) during sternal aspirations, which may cause heart or lung problems and possible need for anesthesia.

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. Male or female subjects, age 18 years or older.
2. Presence of measurable disease that has been confirmed by histology or cytology. Myelofibrosis subjects must have palpable spleen of * 5 cm below the left subcostal margin on physical examination at the screening visit.
3. The following malignancy types will be included in each of the treatment groups:
* Part 1 (Dose Escalation)
Treatment Group A: AML or myelodysplastic syndrome (MDS)
Treatment Group B: SCLC (other solid tumors, eg, endocrine tumors, are allowed with medical monitor approval)
* Part 2 (Dose Expansion)
Treatment Group A1: Relapsed/refractory AML or MDS
Treatment Group A2: MF (PMF, PPV-MF, and PET-MF)
Treatment Group B1: SCLC
Treatment Group B2: Ewing's sarcoma and poorly differentiated neuroendocrine tumors
* Parts 3 and 4 (Combination Dose Escalation/Expansion)
Treatment Group C/C1: Relapsed/refractory AML
Treatment Group D/D1: Newly diagnosed, treatment-naive AML, or MDS who are unfit to tolerate standard intensive chemotherapy at study entry and who are eligible to receive azacitidine as first-line therapy for the disease under study.
Treatment Group E/E1: SCLC previously progressed on platinum-based treatment
4. Subjects must meet specific disease and treatment criteria as follows:
* TG A/A1/A2, TG B/B1/B2, C/C1, and TG E/E1: The subject must not be a

candidate for potentially curative therapy or standard-of-care approved therapy.
* TG A2: The subjects must have confirmed diagnosis of PMF, PPV-MF, or PET-MF according to revised WHO 2016 criteria.
* TG D/D1: Subjects with newly diagnosed, treatment-naive AML who are unfit to tolerate standard intensive chemotherapy at study entry based on at least 1 of the following criteria:
* Age * 75 years old
* History of congestive heart failure (CHF) or documented ejection fraction (EF) * 50%
* Pulmonary disease with diffusing capacity of the lungs for carbon monoxide* 65% or FEVI * 65%, or dyspnea at rest or requiring oxygen
* Any other comorbidity that the physician judges to be incompatible with intensive chemotherapy
OR
Subjects with newly diagnosed, treatment-naïve, IPSS-R intermediate or higher risk disease MDS who have at least 5% bone marrow blasts, who are unfit to tolerate standard intensive chemotherapy at study entry and who are eligible to receive azacitidine as first-line therapy for the disease under study.
The following treatments for prior lower risk MDS are acceptable:
Revlimid®, low-dose cytarabine, and growth factors.
* TG E/E1: The subjects in TG E must have previously received platinum-based therapy, but additional lines of therapies are allowed. The subjects in TG E1 must not have received more than 1 previous line of therapy for locally advanced or metastatic SCLC. The previous line of therapy must be a platinum-based therapy, and the subjects must have progressed on or after this treatment.
5. Willingness to undergo a pretreatment bone marrow biopsy or aspirate (AML/MDS/MF) during screening (may be waived with medical monitor approval). For subjects with solid malignancies, must have baseline archival tumor specimen available: a tumor block or approximately 15 slides from biopsy or resection of primary tumor or metastasis that are < 2 years old (specimens > 2 years old may be accepted with medical monitor approval)., Please refer to study protocol for further inclusion criteria

Exclusion criteria

1. Receipt of anticancer medications, anticancer therapies, or investigational drugs within the following interval before the first administration of study drug (requirement may be waived with medical monitor approval):
a. < 5 half-lives or 14 days, whichever is longer, for any investigational agent
b. < 5 half-lives for all other anticancer medications
c. < 6 weeks for mitomycin-C or nitrosoureas
2. Any unresolved toxicity * Grade 2 from previous anticancer therapy except for stable chronic toxicities (* Grade 2) not expected to resolve.
3. All treatment groups: prior receipt of an LSD1 inhibitor therapy. Parts 3

and 4 TG E/E1: prior receipt of anti*programmed cell death-1, anti*programmed death ligand 1, or anti*PD-L2 antibody.
4. Any of the following laboratory results at screening without transfusions and hematopoietic growth factor support in solid tumors (no lower limits in AML and MDS, or in MF with medical monitor approval):
Absolute neutrophil count (× 109/L): < 1.5
Hemoglobin (g/dL): < 9.0
Platelet count (× 109/L): < 100
5. Laboratory and medical history parameters outside Protocol-defined range unless associated with primary malignancy or metastatic disease and with medical monitor approval:
a. Total bilirubin > 1.5 × institutional upper limit of normal (ULN) if no liver metastases or > 3 × ULN in the presence of liver metastases or presence of documented Gilbert syndrome (unconjugated hyperbilirubinemia).
b. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.0 × institutional ULN.
c. Creatinine clearance < 60 mL/min based on the institutional formula., Please refers to study protocol for further exclusion criteria

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):	11-06-2019
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	INCB059872

Generic name:	INCB059872
Product type:	Medicine
Brand name:	Opdivo
Generic name:	NIVOLUMAB
Product type:	Medicine
Brand name:	Vesanoid
Generic name:	TRETINOIN
Product type:	Medicine
Brand name:	Vidaza
Generic name:	AZACITIDINE

Ethics review

Approved WMO Date:	09-08-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-08-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-11-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-03-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-04-2019
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-08-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-08-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-11-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-11-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-04-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2017-001710-28-NL
CCMO	NL62333.056.17
Other	Unknown for now