An open-label, multi-center, Phase I study of oral IAG933 in adult patients with advanced Mesothelioma and other solid tumors

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This study has been transitioned to CTIS with ID 2023-508369-34-00 check the CTIS register for the current data. The purpose of this first-in-human (FIH) study is to characterize the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Mesotheliomas
Study type	Interventional

Summary

ID

NL-OMON54125

Source
ToetsingOnline

Brief title
CIAG933A12101

Condition

- Mesotheliomas

Synonym
asbestos-cancer, mesothelioma

Research involving
Human

Sponsors and support

Primary sponsor: Novartis

Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: all solids, Hippo pathway, IAG933, mesothelioma

Outcome measures

Primary outcome

Safety: Incidence and severity of Adverse Events (AEs) and Serious Adverse Events (SAEs), including clinically significant changes in laboratory parameters, vital signs, and ECGs. Incidence and nature of dose limiting toxicities (DLTs) during the first cycle of dosing

Tolerability: Dose interruptions, reductions and dose intensity

See also section 2 of the protocol.

Secondary outcome

Overall Response Rate (ORR), disease control rate (DCR), progression-free survival (PFS), duration of response (DOR) as per RECIST v1.1*

Plasma concentration vs. time profiles and derived PK parameters for IAG933 such as Cmax, Tmax, Cmin, AUC, T1/2, Racc

ORR, DCR, PFS, DOR as per RECIST v1.1*

OS

Study description

Background summary

The Hippo pathway is an evolutionarily conserved signaling pathway that plays essential roles in embryonic development, control of organ size, epithelial homeostasis, tissue regeneration, and wound healing. Numerous studies have identified roles for the Hippo pathway in cancer cell migration, invasion, and metastasis.

The core components of the Hippo pathway include neurofibromin 2 (NF2), mammalian sterile 20-like kinases 1 and 2 (MST1/2), large tumor suppressor kinase 1/2 (LATS1/2), two human paralogs, Yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ, also known as WW Domain Containing Transcription Regulator 1), and transcriptional enhancer associate domain (TEAD) family members (Pan 2010). The kinase cascade of the Hippo pathway regulates the activity of the transcriptional coactivators YAP and TAZ, which interact with TEADs to induce target gene transcription (Moroishi et al 2015).

When the Hippo pathway is *on*, MST1/2 phosphorylate and activate LATS1/2, which in turn phosphorylate YAP/TAZ on multiple serine residues, resulting in the binding of 14-3-3, cytoplasmic retention and sequestration, which is then followed by ubiquitination and degradation. When the Hippo pathway is *off*, dephosphorylated YAP/TAZ translocate into the nucleus, bind TEAD, and drive transcription of target genes that are critical for cell growth, proliferation, and survival (Pan 2010).

Hyperactivation of YAP and/or TAZ (and subsequent hyperactivity of the YAP/TAZ-TEAD transcriptional complex) is commonly seen in a number of human cancers (Anon 2017, Muramatsu et al 2011, Eun et al 2017) and high expression and nuclear localization of YAP/TAZ has been associated with poor prognosis and resistance to treatment (Jia 2003, Zanconato et al 2016). High nuclear expression of YAP/TAZ has been found in a variety of cancers including high-grade breast carcinomas and triple-negative breast cancer (Cordenonsi et al 2011, Diaz-Martin et al 2015), as well as in head and neck cancers where it has correlated with tumor recurrence, resistance to radio- and immunotherapy and poor outcomes (Lee et al 2015).

In esophageal cancers, YAP amplification (Anon 2017), and high nuclear localization is a predictor of poor prognosis and resistance to therapy (Muramatsu et al 2011), while YAP-regulated gene expression has been associated with poor prognosis in colorectal cancer (Muramatsu et al 2011, Eun et al 2017). TAZ amplifications have been found in lung squamous cell carcinoma (Jia 2003, Sun et al 2019, Dey et al 2020) and in ovarian cancers (Lamar 2012) In

addition, YAP/TAZ may also be implicated in the development and progression of metastases. Studies indicated that ectopic expression of YAP has potent pro-metastatic activity, particularly nuclear-localized mutants of YAP (Lamar 2012). This activity relies on TEAD binding, suggesting that YAP/TEAD inhibition may offer therapeutic potential in aggressive cancers (Dey et al 2020).

See also section 1 of the protocol.

Study objective

This study has been transitioned to CTIS with ID 2023-508369-34-00 check the CTIS register for the current data.

The purpose of this first-in-human (FIH) study is to characterize the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and preliminary anti-tumor activity of IAG933 in adult patients with advanced mesothelioma or other solid tumors harboring certain molecular alterations in the Hippo pathway. The dose escalation part will include patients with advanced mesothelioma, or solid tumors bearing NF2/LATS1/LATS2 truncating mutations (LATS1/LATS2 mutations will only be included in the dose escalation part) or functional YAP/TAZ fusions. The main purpose of dose escalation is to determine the maximum tolerated dose(s) (MTDs) and/or recommended dose(s) (RDs) and dosing schedule(s) of single agent IAG933. The RD(s) will be further explored in select indications in the expansion part of the study. The purpose of dose expansion is to assess preliminary anti-tumor activity and further explore safety and tolerability of IAG933 at the RD(s). In addition, the study will assess PD changes induced by IAG933 and characterize the PK/PD relationship. Finally, a food effect evaluation of IAG933 may be performed in an exploratory food effect cohort to investigate the effect of food on IAG933 exposure.

See also section 1 of protocol.

Study design

This study is a FIH, open-label, phase I, multi-center study of IAG933 as a single agent, consisting of a dose escalation part followed by a dose expansion part. Dose escalation will be conducted in adult patients with advanced mesothelioma or other solid tumors with specified dysregulations in the Hippo pathway. Upon determination of the MTDs and/or RDs for expansion, the study will continue with an expansion part in defined patient populations.

Initiation of dosing between the first patients (up to the first 3) in a cohort at a daily dose higher than any daily dose previously tested and shown to be safe will be staggered by at least 48 hours.
The study treatment will be administered until the patient experiences

unacceptable toxicity, progressive disease, and/or has treatment discontinued at the discretion of the Investigator or the patient, or due to withdrawal of consent.

An exploratory food effect cohort(s) may be included to assess IAG933 PK properties, safety and tolerability in patients under fed conditions.

See also section 3 of the protocol

Intervention

For this study, *investigational drug* and *study treatment* refer to IAG933. The investigational drugs used in this study are listed in Table 6-1 in the protocol. Additional drug strengths may become available and be used in this study.

See also section 6 of the protocol.

Study burden and risks

Risks and sideeffects assocated with the treatment (IAG933) and the tests necessary to track the patients suchs as blooddraws, imaging and tumor biopsies.

The burden of participtating consists of the following:
For dosing 3don/4doff:
Cycle 1: 1 visit of 3 days and 5 visits of 1 day
Cycle 2: 4 visits
Cycle 3-6: 2 visits
From cycle 7: 1 visit

For continous dosing:
Cycle 1: 1 visits of 3 days, 4 visits of 1 day
Cycle 2: 4 visits
Cycle 3-6: 2 visits
From cycle 7: 1 visit

Most visits will be 2-4 hours long, PK days (day 1 and day 15 of cycle 1) will be at minimum 12 hours long. The start of the study in both schedules has tests on day 1, 2 and 3. Patients can go home at the end of day 1 and 2, or can use alternative accomodations near the hospital if they do not need to be observed by research staff due to adverse events.

During the visits, the following tests might be performed, the frequency and number of tests will depend on the type of visit and the schedule for dosing: physical exams, blooddraws, urine collection, Holter research, ECGs,

echocardiogram, imaging, pregnancy tests (for women who can get pregnant), tumor and skin biopsies.

Contacts

Public
Novartis

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Scientific
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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.Signed informed consent must be obtained prior to participation in the study.
2. Male or female patients must be >= 18 years of age
3. (dose escalation) Patients with histologically or cytologically confirmed diagnosis of advanced (unresectable or metastatic) mesothelioma or other solid tumors. Patients with solid tumors other than mesothelioma must have local available data for loss-of-function NF2/LATS1/LATS2 genetic alterations (truncating mutation or gene deletion; LATS1/LATS2 mutations will only be included in the dose escalation part), or functional YAP/TAZ fusions (see

Appendix 4 for requirements for molecular alterations). Patients with malignant EHE can be enrolled with only histological confirmation of the disease. Patients must have failed available standard therapies, be intolerant of or ineligible for standard therapy, or for whom no standard therapy exists.
4. Dose expansion part: the following patients will be enrolled into 3 different treatment groups:
Group 1: Advanced (unresectable or metastatic) MPM patients who have failed available standard therapies for advanced/metastatic disease, be intolerant or ineligible to receive such therapy, or for whom no standard therapy exists.
Group 2: Advanced (unresectable or metastatic) solid tumor patients with available local data for NF2 truncating mutation or deletions (refer to Appendix 4 for more details). Patient must have failed available standard therapies, be intolerant or ineligible to receive such therapy, or for whom no standard therapy exists.
Group 3: Advanced (unresectable or metastatic) solid tumor patients with available local data for functional YAP/TAZ fusions (refer to Appendix 4 for more details). EHE patients can be included with only histological confirmation of the disease. Patient must have failed available standard therapies, be intolerant or ineligible to receive such therapy, or for whom no standard therapy exists.
5. Presence of at least one measurable lesion according to mRECIST v1.1 (for mesothelioma patients, refer to Appendix 2), RECIST v1.1 (for patients with other solid tumors, refer to Appendix 1), or RANO (for patients with primary brain tumors, refer to Appendix 3).
6. Patient must have a site of disease amenable to biopsy and be a candidate for tumor biopsy according to the treating institution*s guidelines. Patient must be willing to undergo a new tumor biopsy at screening/baseline, and again during therapy on this study. Archival tissue obtained within 3 months and after last systemic treatment may be used at screening. Exceptions may be considered after documented discussion with Novartis.
7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

Exclusion criteria

1. Treatment with any of the following anti-cancer therapies prior to the first dose of study treatment within the stated timeframes:
a. <= 4 weeks for thoracic radiotherapy to lung fields or limited field radiation for palliation within <= 2 weeks prior to the first dose of study treatment. An exception to this exists for patients who have received palliative radiotherapy to bone, who must have recovered from radiotherapy-related toxicities but for whom a 2-week washout period is not required.
b. <= 4 weeks or <= 5 half-lives (whichever is shorter) for chemotherapy or biological therapy (including monoclonal antibodies) or continuous or intermittent small molecule therapeutics or any other investigational agent.

c. <= 6 weeks for cytotoxic agents with risk of major delayed toxicities, such as nitrosoureas and mitomycin C.
d. <= 4 weeks for immuno-oncologic therapy, such as CTLA4, PD-1, or PD-L1 antagonists
e. Prior treatment with TEAD inhibitor at any time
2. For mesothelioma patients: use of non-invasive antineoplastic therapy (e.g., tumor treating fields, brand name Optune LuaTM) within 2 weeks of the tumor assessment at screening.
3. Malignant disease, other than that being treated in this study. Exceptions to this exclusion include the following: malignancies that were treated curatively and have not recurred within 2 years prior to study entry; completely resected basal cell and squamous cell skin cancers; any malignancy considered to be indolent and that has never required therapy; and completely resected carcinoma in situ of any type.
4. Presence of symptomatic CNS metastases, or CNS tumors or metastases that require local CNS-directed therapy (such as radiotherapy within 3 months of tumor assessment at screening or surgery), or increasing doses of corticosteroids 2 weeks prior to study entry.
Patients with treated symptomatic brain tumors should be neurologically stable (for 4 weeks post-treatment and prior to study entry) and at a dose of <= 10 mg per day prednisone or equivalent for at least 2 weeks before administration of any study treatment
5. Patients who have undergone major surgery <= 4 weeks prior to first dose of study treatment
6. History of allogeneic bone marrow or solid organ transplant.
7. Insufficient renal function at Screening:
a. Serum creatinine > 1.5 x ULN
b. Estimated glomerular filtration rate (eGFR) < 50 mL/min/1.73m2 (calculated using the Cockcroft-Gault formula, or the CKD-EPI Creatinine-Cystatin C formula as listed in Appendix 7).
c. Urine protein-creatinine ratio > 0.5 g/g (56.5 mg/mmol)
8. Clinically significant cardiac disease or risk factors at screening, including any of the following:
a. Clinically significant and/or uncontrolled heart disease, including coronary artery disease, uncontrolled hypertension, clinically significant arrhythmia, and congestive heart failure (NYHA grade >= 2).
b. Acute myocardial infarction or unstable angina pectoris within 6 months prior to study entry.
c. Left ventricular ejection fraction (LVEF) < 50% as determined by Cardiovascular magnetic resonance imaging (cardiac magnetic resonance imaging (MRI)) or trans-thoracic echocardiography (TTE).
d. Resting QTcF >=450 msec (male) or >=460 msec (female) at screening, or QTc not assessable
e. Resting heart rate (physical exam or 12 lead ECG) < 50 bpm
f. PR interval >200ms, Mobitz type II second degree AV block, high-grade AV block or third degree (complete) AV block
g. Risk factors for Torsades de Pointes (TdP), including uncorrected

hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia, or any of the following:
i. History of familial long QT syndrome, known family history of TdP or family history of idiopathic sudden death
ii. Concomitant QT prolonging medication(s) with a known risk of QT prolongation that cannot be discontinued or replaced by safe alternative medications at least 7 days prior to the start of study treatment and for the duration of the study (see Appendix 5)
9. Insufficient bone marrow function at screening:
a. Absolute Neutrophil Count (ANC) < 1.5 x 109/L
b. Hemoglobin < 9.0 g/dL without transfusion support within 7 days prior to start of study treatment
c. Platelet count < 75 x 109/L without transfusion support within 7 days prior to start of study treatment
10. Insufficient hepatic function at screening:
a. Serum total bilirubin > 1.5 x upper limit of normal (ULN). An exception is for patients with Gilbert*s syndrome, who are excluded if total bilirubin > 3.0 x ULN and direct bilirubin >1.5 x ULN.
b. Aspartate aminotransferase (AST) > 3 x ULN or > 5 x ULN if liver metastases are present.
c. Alanine aminotransferase (ALT) > 3 x ULN or > 5 x ULN if liver metastases are present.
11. Patients who have the following laboratory values outside of the laboratory normal limits (treatment may be given during screening to correct values):
a. Potassium
b. Magnesium
c. Total calcium (corrected for low serum albumin)

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	03-03-2023

Enrollment:	10
Type:	Actual

Medical products/devices used

Registration:	No

Ethics review

Approved WMO Date:	05-08-2022
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-12-2022
Application type:	First submission
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:	05-06-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-10-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-11-2023
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	CTIS2023-508369-34-00
EudraCT	EUCTR2021-000383-30-NL
ClinicalTrials.gov	NCT04857372
CCMO	NL79021.078.22