A phase I/II, multicenter, open-label study of MAK683 in adult patients with advanced malignancies

Published: 08-01-2018
Last updated: 12-04-2024

Primary: Part 1: Safety and tolerability. Determine the MTD and/or RP2D of MAK683.Part 2: Anti-tumor activity of MAK683.Secondary: Part 1: Anti-tumor activity. Pharmacodynamics (PD). Pharmacokinetics (PK).Part 2: Safety and tolerability. PK, PD.

Ethical review	Approved WMO
Status	Will not start
Health condition type	Haematopoietic neoplasms (excl leukaemias and lymphomas)
Study type	Interventional

Summary

ID

NL-OMON46802

Source
ToetsingOnline

Brief title
CMAK683X2101 fase I/II study in advanced malignancies

Condition

- Haematopoietic neoplasms (excl leukaemias and lymphomas)
- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
Lymphoma and solid tumors

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Diffuse large B-Cell Lymphoma, EZH2 mutation, Follecular Lymphoma, MAK683

Outcome measures

Primary outcome

Phase 1

Safety: DLTs, Incidence and severity of AE's and serious AE's,

Tolerability: Dose interruptions, reductions and dose intensity

Phase 2 : Overall response rate (ORR).

Secondary outcome

Phase I part

Overall Response Rate (ORR), Duration of Overall Response (DOR),

Progression-FreeSsurvival PFS) and Best Overall Response (BOR).

PK parameters, pre- and posttreatment expression of H3K27 tri methylationin

PBsMC

Phase II part

DOR, PFS and BOR

Safety: DLTs, Incidence and severity of AE's and serious AE

Tolerability: Dose interruptions, reductions and dose intensity

PK parameters

Pre- and post treatment expression of H3K27 tri methylation in PBMC

Study description

Background summary

PRC2 is an important methyltransferase complex that modifies the epigenetic status of target genes such as tumor suppressor genes, DNA repair genes and cell cycle control genes. EZH2 in conjunction with EED-subunits of PRC2 functions as a histone methyltransferase for H3K27 and in turn repressing target genes.
EZH2 overexpression has been shown to contribute to neoplastic transformation, tumor aggressiveness and portends a poor prognosis in several tumor types including lymphoma, Nasopharyngeal carcinoma, prostate cancer, ovarian cancers, gastric tumors and multiple solid tumor malignancies.
MAK683 is a selective, potent and first-in -class EED inhibitor and has demonstrated in vitro inhibitory activity and in vivo anti-tumor activity in several preclinical tumor models, including DLBCL, nasopharyngeal carcinoma and other solid tumors.

Study objective

Primary:
Part 1: Safety and tolerability. Determine the MTD and/or RP2D of MAK683.
Part 2: Anti-tumor activity of MAK683.

Secondary:
Part 1: Anti-tumor activity. Pharmacodynamics (PD). Pharmacokinetics (PK).
Part 2: Safety and tolerability. PK, PD.

Study design

Phase I/II, multi-center, open-label dose escalation and dose expansion study.
Prescreening (tumor tissue) for subjects with DLBCL and nasopharyngeal carcinoma.
Food-effect study in 12 patients
Appr. 148 subjects (100 phase 2 part).Treatment until disease progression or unacceptable toxicity.

Intervention

Treatment with MAK683.
Oral intake QD. other schedules may be explored.

Study burden and risks

Possible Adverse effects of MAK683 (based on animal studies)

- Side effects related to digestive system, blood cell count and function, liver and skin were seen in animal studies. Most of the abnormalities seen in animals got better after stopping treatment with MAK683.
- An increase in heart rate was observed in dog following single high dose.
- Based on these results of animal studies the most likely and most severe side effects of MAK683 are expected to include effects such as vomiting, diarrhea and bodyweight loss.
- In dogs and rats studies, side effects were also observed in the male reproductive organ (testis) which were not reversed during the 4 week recovery period after stopping treatment. The animals were not observed beyond this 4 week period. It is however, not known whether MAK683 has any effect on the testis in humans.

Risks and inconveniences of the assessments as radiation, bleeding after blooddraw and/or tumorbiopsy

Burden:
Cycles of 4 weeks. cycle 1: 6 visits,, cylce 2: 5 visits, subsequent cycles: 2 visit each cycle.
Physical examination: every visit.
Blood tests: 4 times (cycle 1,2), 2 times (cycle 3,4), once (cycle 5 onwards); 3-18 mL/occasion plus PK and biomarkers (160 ml in total).
Pregnancy test: every cycle.
ECG: .phase 1: 6x cycle 1 day 1 and 6x cycle 1 day 8, 4x cycle 2, thereafter 1x each cycle and at end of treatment.
Echocardiogram or MUGA: 3 times.
Abdominal ultrasound (liver and biliary tract): 3 times.
Tumor measurements: baseline, cycle 3 and every 8 weeks thereafter. During follow up for progression every 8-12 weeks.
Tumor biopsy once at baseline and at cycle 1 day 15 (optional for patients with DLBCL).
Two optional skinbiopsies (prior to first dose of MAK683 and on-treatment Cycle 1)

Contacts

Public
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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

- ECOG performance status 0 to 2
- Patients progressed after standard therapy or are intolerant of standard therapy or for whom no standard therapy exists
- Measurable disease according to RECIST v1.1 for patients with solid tumors or Cheson criteria for patients with DLBCL
- Patients must have a site of disease amenable for biopsy. On-Treatment biopsy (C1D15) is required for patients with solid tumors
- Histologically or cytologically confirmed diagnosis required for all indications
- Patients with DLBCL: documentation of EZH2 mutational status required in phase II
- Patients with NPC: documentation of presence of p16/CDKN2A gene required
- Patients with ovarian cancer must have a primary tumor wiith great than 50% clear cell histomorphology
- Patients with prostate cancer must have evidence of castration resistance: a confirmed rising PSA and a castrate-serum testosterone level (i.e. * 50 mg/dL);
- Patients with sarcoma: Enrollment is limited to epithelioid sarcoma, other types of sarcoma with SWI/SNF alterations may be considered with approval from Novartis.;Other protocol inclusion criteria may apply (section 5.2)

Exclusion criteria

- Other malignant disease than the one being treated in this study

- Severe and/or uncontrolled medical conditions that in the investigator*s opinion could affect the safety of individual or impair the assessment of study result.
- B-cell lymphoma patients who have received prior allogeneic stem cell transplant
- Patient have received anti-cancer therapies within defined time frames prior to the first dose of study treatment (protocol section 5.3 bullet 10)
- CNS involvement which are neurologically unstable or requiring increasing doses of steroids to control.
- Insufficient bone marrow function at screening: Platelets * 50 x 109/L (50,000/mm3) - Hemoglobin (Hgb) * 90 g/L (9 g/dL) - Absolute neutrophil count (ANC) * 1.0 x 109/L (1000/mm3)
- Insufficient hepatic and renal function at screening: ALP, ALT, and AST > 3 x ULN (>5 x ULN if subject has liver metastases) - Total bilirubin *2 x ULN - Serum creatinine > 1.5 x ULN and/or creatinine clearance * 50 mL/min
- Unable to stop any prohibited medications, including strong CYP3A4 inhibitors or inducers, CYP3A4 or CYP2C8 substrates with a narrow therapeutic index, long acting proton pump inhibitors.;Other protocol-defined exclusion criteria may apply (protocol section 5.3)

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	4
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Nog niet van toepassing
Generic name:	Nog niet van toepassing

Ethics review

Approved WMO Date:	08-01-2018
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	18-05-2018
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	19-11-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	19-12-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	15-10-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	01-05-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	EUCTR2016-001860-12-NL
ClinicalTrials.gov	NCT02900651
CCMO	NL63879.041.17