A Phase 1 Study to Evaluate the Safety, Tolerability and Efficacy of MK-8353 Combination Therapies in Subjects With Advanced Solid Tumors

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To determine the dose-limiting toxicities (DLTs) and maximum tolerated dose (MTD) of MK-8353 administered orally in combination with other agents to adult subjects with advanced tumors and to determine the recommended Phase 2 dose (RPTD) of MK-8353...

Ethical review	Approved WMO
Status	Pending
Health condition type	Gastrointestinal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON37039

Source
ToetsingOnline

Brief title
MK8353-010

Condition

- Gastrointestinal neoplasms malignant and unspecified

Synonym
advanced solid tumor

Research involving
Human

Sponsors and support

Primary sponsor: Merck Sharp & Dohme (MSD)

Source(s) of monetary or material Support: Merck Sharp & Dohme Corp.

Intervention

Keyword: Advanced solid tumor, Colorectal cancer, MK8353

Outcome measures

Primary outcome

The goal of this study is to evaluate the safety, tolerability and PK parameters of MK-8353 in combination with three different anti-cancer agents (3 arms of combinations). The dose escalation and confirmation of the MTD will be done using a design based on Toxicity Probability Interval (TPI) for each arm of this study.

Secondary outcome

Not applicable

Study description

Background summary

Extracellular regulated kinase (ERK)1 and ERK2 are closely related serine-threonine protein kinases. They are components of the RAS/mitogen-activated protein kinase (MAPK) pathway, a critical signal transduction pathway that is activated in response to growth factor binding and regulates cellular growth, differentiation and survival in a variety of cell types. ERK lies downstream from the small guanosine triphosphatase (GTPase) RAS and the protein kinases RAF and MEK in this pathway. Following its activation by RAS, RAF phosphorylates MEK1 and MEK2, which in turn phosphorylate ERK. Activated, phosphorylated ERK (pERK) phosphorylates other substrates that govern the transcriptional output of cells. Constitutive activation of this pathway is frequently observed in human cancers and is associated with high rates of cancer cell proliferation. Commonly, pathway activation occurs as a consequence of gain-of-function oncogenic mutations in RAS or in one of the RAF kinase family members, e.g., BRAF. The high frequency of RAS or BRAF mutations in many cancers makes targeting this pathway an attractive strategy

for cancer therapy. Activating mutations of RAS are reported in ~25% of all cancers, with some, such as pancreatic and colorectal cancer, harboring KRAS mutation rates of ~90% and ~50%, respectively. NRAS mutations have been identified in ~10-25% of melanomas and KRAS mutations have been identified in ~30% of non-small cell lung cancers (NSCLCs).
BRAF somatic missense mutations have been identified in ~50-70% of malignant melanomas, where all mutations are within the kinase domain and a single substitution (V600E, previously designated V599E) accounts for ~80% of mutations. Activating BRAF mutations have also been documented in a variety of human cancers, including colorectal cancer (CRC; ~10-12%), NSCLC (2-3%), and thyroid cancer (~50%).
With very few exceptions, BRAF and RAS mutations are mutually exclusive.

MK-8353 is a highly selective, orally available, adenosine triphosphate (ATP) competitive small molecule inhibitor of ERK. MK-8353 not only inhibits the kinase activity of ERK, but induces a conformational change in ERK that prevents its phosphorylation and activation by MEK. This unique property of MK-8353 enables the phosphorylation status of ERK to serve as one of the target engagement biomarkers for MK-8353 action. To date, there are no known ERK inhibitors in clinical development.
MK-8353 potently inhibits both ERK1 and ERK2 in vitro with IC50 values of 23.0 nM and 8.8 nM, respectively. MK-8353 caused a dose-dependent decrease in pERK1, pERK2, and pRSK (phosphorylated p90 ribosomal S6 kinase) levels with complete suppression of pERK1
and pERK2 at 30 nM in BRAF mutant A2058 cells. Also, the anti-proliferative effects of MK-8353 were characterized against a large panel of tumor cells. MK-8353 potently inhibited the growth of BRAF mutant melanoma cell lines, and also inhibited growth of BRAF mutant CRC and thyroid cancer cell lines. In addition, MK-8353 inhibited the growth of KRAS mutant colon, pancreatic, and NSCLC tumor cell lines and NRAS mutant melanoma cell lines. Inhibition of pERK by MK-8353 correlated with inhibition of cell proliferation and induction of apoptosis in vitro. The efficacy of the ERK inhibitor MK-8353 as a single agent was tested in a panel of BRAF and K/NRAS mutant mouse xenograft models. MK-8353 inhibited tumor growth and induced tumor regression in both BRAF mutant and K/NRAS mutant mouse xenograft models. These results further confirm the in vitro studies showing that tumor cells harboring BRAF or K- or NRAS mutations are sensitive to MK-8353.

Study objective

To determine the dose-limiting toxicities (DLTs) and maximum tolerated dose (MTD) of MK-8353 administered orally in combination with other agents to adult subjects with advanced tumors and to determine the recommended Phase 2 dose (RPTD) of MK-8353 based on safety, tolerability, and pharmacokinetics.

Study design

This is a multicenter, worldwide, open label, non-randomized, Phase I study of MK-8353 in combination with FOLFIRI administered in subjects with KRAS mutant colorectal cancer, or in combination with MK-8669 or MK-3475, respectively, administered in subjects with advanced solid tumors. In addition in MK-8353 + MK-3475 arm, KRAS mutant NSCLC and NRAS/BRAF mutant melanoma subjects will be enrolled at the MTD to further evaluate efficacy. The goal of this study is to evaluate the safety, tolerability and PK parameters of MK-8353 in combination with three different anti-cancer agents (3 arms of combinations).
The dose escalation and confirmation of the MTD will be done using a design based on Toxicity Probability Interval (TPI) for each arm of this study.
Cohorts of 3 subjects will initially be enrolled sequentially on rising dose levels of MK-8353 with a fixed dose levels of FOLFIRI or MK-3475, or with appropriately adjusted dose levels of MK-8669. Barring dose limiting toxicities, additional subjects will be enrolled, and dose-finding will proceed according to an algorithm based on TPI, targeting a 25% dose limiting toxicities (DLT) rate for MK-8353 in combination with MK-8669 or MK-3475, and a 30% DLT rate for MK-8353 in combination with FOLFIRI, until an MTD of each combination is determined . Approximately 150 subjects evaluable for safety and tolerability will be enrolled. The final number will depend on safety data and observed DLTs.

Intervention

Study visits, administration of MK-8353, administration of Folfiri, MK-8669 or MK-3475, completion of a dosingdiary, avoid to consume grapefruit or star fruit for 2 weeks before the first dose of MK-8353 combinations and for the entire duration of the study, physical examination, ECG, checking of vital signs, provide tumor biopsy (optional), bloed draw and collection of urine sample.

Study burden and risks

Possible side effects of MK-8353, MK-8669 or MK3475.
Risk's of blood draw, ECG, infusion, CT-scans, MRI and biopsy.

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. Be willing and able to provide written informed consent for the trial.
2. Have one of the following pathologically/histologically confirmed cancer types to be eligible for each study arm:;a. Arm A: metastatic CRC with a KRAS mutation in their tumor sample,
progressed during or within 6 months of the last dose of a prior chemotherapy,
and FOLFIRI treatment is indicated in the opinion of the investigator;;•* Subjects must agree to provide archival tumor tissue sample or newly
obtained tumor biopsy sample if archived tissue is unavailable for
analysis of KRAS mutation to determine eligibility.;b. Arms B & C: any advanced solid tumor (metastatic or locally advanced
disease) that has failed to respond to curative therapy, progressed despite
curative therapy, or for which curative therapy is not available.;•* For Arm C: a subset of subjects enrolled at the maximum tolerated
dose (MTD) must have either NRAS/BRAF mutant melanoma or
KRAS mutant NSCLC. In this subset, subjects must agree to provide
archival tumor tissue sample or newly obtained tumor biopsy sample if
archived tissue is unavailable for analysis of KRAS/NRAS/BRAF
mutation to determine eligibility.;3. Have at least one measurable lesion, as defined by Response Evaluation Criteria in
Solid Tumors (RECIST v1.1). If the subject has received radiation therapy, at least
one measurable lesion must be outside the area of radiation, or at least one
measurable lesion must be progressing inside the area of radiation.;4. Be able to swallow, retain, and absorb oral medications and oral nutrition.;5. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.;6. Demonstrate adequate organ

function as defined by the following table, all screening
labs should be performed within one-two weeks of treatment initiation. Be able to adhere to dose and visit schedules.;8. Each female subject of childbearing potential must have a negative urine or serum
pregnancy test. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. The serum pregnancy test must be negative for the subject to be eligible.;9. Each female subject who is not free from menses for >2 years, post hysterectomy /
oophorectomy, or surgically sterilized, must be willing to use either 2 adequate barrier methods or a barrier method plus a hormonal method of contraception to prevent pregnancy or to abstain from heterosexual activity throughout the study, starting with Visit 1 through 90 days after the last dose of study therapy. Approved contraceptive methods include, for example: intra uterine device, diaphragm with spermicide, cervical cap with spermicide, male condoms, or female condom with spermicide. Spermicides alone are not an acceptable method of contraception.
Each male subject must agree to use an adequate method of contraception or abstain from heterosexual intercourse with a partner who could become pregnant starting with the first dose of study drug through 90 days after the last dose of study therapy.

Exclusion criteria

• Has unstable or progressing central nervous system (CNS) metastasis. Subjects with known CNS metastasis may be included if the subject is asymptomatic for 1 month with no requirement for steroids or antiseizure medications.
• Has active gastrointestinal disease or a disorder or a history of surgery that significantly alters gastrointestinal motility or absorption in the opinion of the investigator.
• Has received ERK inhibitors for the disease under study.
• For Arm A: The subject has a known dihydropyrimindine dehydrogenase (DPD) deficiency or known UGT1A1*28 polymorphism.
• For Arm C:
- The subject has received prior therapy with an anti-PD-1 or anti PD-L1 antibody.
- The subject has an active autoimmune disease or a documented history of autoimmune disease, except vitiligo or resolved childhood asthma/atopy
- The subject is on chronic systemic steroid therapy or on any other form of immunosuppressive medication.
• Has a known hypersensitivity to MK-8353, irinotecan (Arm A), leucovorin (Arm A), 5-FU (Arm A), MK-8669 (Arm B), MK-3475 or any other mAb (Arm C) or their components.
• Has received any treatment more recently than the indicated washout period prior to the start of treatment with MK-8353 combinations, or must continue to receive any treatment listed in the exclusion medication list during the current trial.
• Has clinically relevant cardiovascular, hepatic, neurologic, endocrine, or other major systemic diseases that would make implementation of the protocol difficult.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	03-12-2012
Enrollment:	24
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Fluorouracil
Generic name:	Fluorouracil
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Irinotecan HCl-3-water
Generic name:	Irinotecan HCl-3-water
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	08-01-2013
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	24-01-2013
Application type:	First submission

Review commission:	METC NedMec
Approved WMO Date:	18-04-2013
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-07-2013
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-12-2013
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-02-2014
Application type:	Amendment
Review commission:	METC NedMec

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	EUCTR2012-002695-13-NL
CCMO	NL41947.031.12
Other	Nog niet bekend