An Open-Label Study of the Safety, Tolerability, and Pharmacokinetic/Pharmacodynamic Profile of M4344 (formerly VX-803) as a Single Agent and in Combination With Cytotoxic Chemotherapy in Participants With Advanced Solid Tumors

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Primary Objective part A:* To evaluate the safety and tolerability of multiple ascending doses of single-agent M4344 administered BIW in subjects withadvanced solid tumors* To determine the MTD and/or RP2D of single-agent M4344 administered BIW in...

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

Summary

ID

NL-OMON50338

Source
ToetsingOnline

Brief title
Study of M4344 in Participants With Advanced Solid Tumors

Condition

- Other condition
- Lymphomas Hodgkin's disease

Synonym

Solid tumors

Health condition

advanced solid tumors

Research involving
Human

Sponsors and support

Primary sponsor: Merck
Source(s) of monetary or material Support: Merck KGaA

Intervention

Keyword: Cancer, M4344, Open-label, Phase I

Outcome measures

Primary outcome

PART A:

- Safety parameters, including adverse events (AEs), clinical laboratory values

(serum chemistry and hematology), vital signs, and

electrocardiogram (ECG) assessments

- MTD and/or RP2D of single-agent M4344 administered BIW

PART A2:

- Safety parameters, including adverse events (AEs), clinical laboratory values

(serum chemistry and hematology), vital signs, and

electrocardiogram (ECG) assessments

- MTD and/or RP2D of single-agent M4344 administered with a twice daily or once

daily dose schedule

PART A3:

- Safety parameters, including AEs, clinical laboratory values (serum chemistry and hematology), vital signs, and ECG assessments
- MTD and/or RP2D of single agent M4344 administered with a drug holiday schedule.

PART B1:

- Safety parameters, including adverse events (AEs), clinical laboratory values (serum chemistry and hematology), vital signs, and electrocardiogram (ECG) assessments
- MTD and/or RP2D of M4344 administered in combination with carboplatin

PARTS C:

1) Occurrence of:

o Treatment-emergent adverse event (TEAEs) and treatment-related AEs graded according to National Cancer Institute Common Terminology Criteria for Adverse Events Laboratory abnormalities

o Clinically significant abnormal vital sign

o Clinically significant abnormal ECG

2) Objective response (i.e. confirmed complete response [CR] or partial response [PR]) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 assessed by the Investigator

Secondary outcome

Part A:

- PK parameter estimates of single-agent M4344 administered BIW, derived from plasma concentration-time data

- Objective tumor response (OR) and disease stabilization (SD) as evaluated by Response Criteria Evaluation (Response Evaluation Criteria in Solid Tumors [RECIST] 1.1

Part A2:

- PK parameteer estimates of single-agent M4344 administered with a twice daily or once daily dose schedule, derived from plasma concentration-time data

- OR and disease stabilization as evaluated by RECIST 1.1

Part A3:

- PK parameter estimates of single agent M4344 (and metabolites as appropriate) administered with a drug holiday dose schedule, derived from plasma concentration time data

- OR and disease stabilization as evaluated by RECIST 1.1

Part B1:

- PK parameter estimates of M4344 administered in combination with carboplatin derived from plasma concentration-time data

- OR as evaluated by Response Criteria Evaluation RECIST 1.1

Parts C:

- OR as evaluated by RECIST 1.1

- PFS

- OS

- DOR

- PK parameter estimates of M4344 (and metabolites as appropriate) in

individual participants with loss-of-function mutations)

- Time matched PK concentrations and digital ECG measures

Study description

Background summary

Merck KGaA is currently developing M4344, a potent and selective inhibitor of ATR (inhibition constant [Ki]<150 pM) with a concentration resulting in 50% maximal inhibition (IC50) of 8 nM for the treatment of advanced malignancies. M4344 sensitizes many human cancer cell lines to the cytotoxic effects of various DNA-damaging agents. In contrast, extensive studies with other ATR inhibitors have shown that noncancer cells tolerate ATR inhibition with only a reversible increase in growth arrest attributable to activation of compensatory, ATM-mediated, DNA repair signaling8.

M4344 has shown efficacy and was well tolerated in mouse xenograft models both as a single agent and in combination with DNA-damaging agents. In mouse xenograft models derived from human cancer cell lines and patient-derived explants, orally administered M4344 markedly
enhanced the antitumor activity of the DNA-damaging agent cisplatin, carboplatin, and gemcitabine. In a mouse xenograft model of triple negative breast cancer, M4344 dosed once weekly potentiated the efficacy of carboplatin, and dosing of this combination led to complete tumor growth inhibition in contrast to dosing of either agent alone.

Mutations in specific Deoxy ribonucleic acid damage response related genes (including ARID1A, ATRX/DAXX and ATM) have been shown to increase reliance on ATR signaling for tumor cell survival and growth. Published data suggest that loss-of-function mutations in specific tumor genes involved in the Deoxy ribonucleic acid (DNA) damage repair process as candidates to predict

sensitivity to ATR inhibitors as monotherapy. Williamson and co-authors showed in an ribonucleic acid interference screening in cell lines that ARID1A was the top hit gene that was synthetically lethal with the ATR inhibitor VX-821, and that there was a noticeable statistically significant difference in sensitivity to M6620 (VX-970) between the ARID1A wild type and mutated xenografts. Flynn and coauthors demonstrated in vitro and in vivo that tumor cells preserving chromosome integrity throughout the alternative lengthening of telomere process, a mechanism associated with loss-of-function mutations in either the genes ATRX or DAXX which involves DNA homologous recombination, are sensitive to ATR inhibition. Antitumor activity of M4344 as monotherapy has been shown in preclinical xenograft harboring such mutations. The co-inactivation of the protein kinase ataxia telangiectasia mutated (ATM) and Rad3-related (ATR) functions results in synthetic lethality, which has been shown in a gastric cancer xenograft model carrying a mutation in ATM with the ATR inhibitor AZD6738. Together, these data support the rationale that patients with solid tumors harboring loss-of-function mutations in ARID1A, ATRX or DAXX, and ATM may benefit from treatment with M4344 monotherapy, independent of anatomic tumor localization.

Study objective

Primary Objective part A:
* To evaluate the safety and tolerability of multiple ascending doses of single-agent M4344 administered BIW in subjects with advanced solid tumors
* To determine the MTD and/or RP2D of single-agent M4344 administered BIW in subjects with advanced solid tumors

Secondary Objectives part A:
* To evaluate PK of single-agent M4344 when administered BIW in subjects with advanced solid tumors
* To assess potential antitumor activity of single-agent M4344 when administered BIW in subjects with advanced solid tumors

Primary Objectives part A2:
* To evaluate the safety and tolerability of multiple asc. doses of single-agent M4344 administered in once or twice daily dose
* To determine the MTD and/or RP2D of single-agent M4344 administered in once or twice daily dose

Secondary Objectives part A2:
* To evaluate PK of single-agent M4344 when administered once or twice daily
* To assess potential antitumor activity of single-agent M4344 when administered once or twice daily

Primary Objectives part A3:

* To evaluate the safety and tolerability of multiple asc. doses of single agent M4344 when administered in a drug holiday dose schedule
* To determine the MTD and/or RP2D of single agent M4344 administered in a drug holiday dose schedule

Secondary Objectives part A3:
* To evaluate PK of single agent M4344 when administered in a drug holiday dose schedule
* To assess preliminary antitumor activity of single agent M4344 when administered in a drug holiday dose schedule

Primary Objective part B1:
* To evaluate the safety and tolerability of M4344 when administered in combination with carboplatin
* To determine the MTD and/or RP2D of M4344 administered in combination with carboplatin

Secondary Objective part B1:
-To evaluate the PK profile of M4344 when admin. in combin. with carboplatin
-To evaluate potential antitumor activity after admin. M4344 in combin. with carboplatin

Primary Objectives Parts C:
* To evaluate the safety, tolerability and efficacy in terms of confirmed OR of M4344 administered at doses and schedules determined as RP2D in Parts A, A2 or A3 in participants with solid tumor harboring loss-of-function mutations in the genes ARIDA (Part C1, C4), ATRX and/or DAXX (Part C2, C5), or ATM (Part C3, C6).

Secondary Objectives Parts C:
- To further evaluate efficacy in terms of confirmed best overall response, duration of response, progression free survival and overall survival time of M4344 when administered in participants with loss-of-function mutations in the genes ARID1A (Part C1, C4), ATRX and/or DAXX (Part C2, C5), or ATM (Part C3, C6).
- To evaluate the PK of M4344 (and metabolites as appropriate) in individual participants with loss-of-function mutations.

Objective Sub-study:
This study will investigate the PDPd of M4344 using clinical biomarkers. Paired tumor biopsies (optional, Parts A2, A3, B1, C) in a tumor biopsy substudy and serial PBMC samples (Parts A2, A3, C) will be collected to evaluate markers of ataxia talangiectasia mutated and Rad3-related protein (ATR) activation and inhibitation, as well as of deoxy ribonucleic acid (DNA) damage.

Study design

This is an open-label Phase I, first-in-human clinical study conducted in multiple Parts (Parts A, A2, A3, B1, C1, C2, C3, C4, C5 and C6).

Intervention

Part A:
Subjects will be administered M4344 BIW (dosed twice-weekly) as a single agent on Days 1, 4, 8, 11, 15, and 18 of a 21-day cycle.
Starting dose 10mg. The dose of M4344 may be increased by up to 100% in a subsequent subject, depending on
toxicities and tolerabilities observed.

Part A2:
Participants in Part A2 will initially be administered M4344 as a single agent BID on a daily regimen. The M4344 starting dose in Part A2 will be 100 mg (single dose) administered BID (200 mg daily).

Part A3:
Participants in Part A3 will be administered M4344 as a single agent in a dose holiday schedule (3 days of dosing followed by 4 days of pausing [3d+/4d-] or 5 days of dosing followed by 2 days of pausing [5d+/2d-] or 7 days of dosing followed by 7 days of pausing [7d+/7d-]) or 14 days of dosing followed by 7 days of pausing [14d+/7d-]).

Part B1:
For each M4344 dose level tested, subjects will receive carboplatin on Day 1, and M4344 on Days 2 and 9 of a 21-day cycle.

Study Parts C will be expansion cohorts to explore potential antitumor efficacy and to confirm the safety and tolerability of single agent M4344 administered at a dose and schedule that has been determined as RP2D in study Part A, A2 or A3.

Study burden and risks

As this is a First in Human study, the risks of the IP for humans are still unknown.
Based on studies done in animals, the study drug, may cause the following adverse events
Changes in numbers of some blood cell types, including Red Blood Cells, White Blood Cells, and platelets.
Nausea, vomiting, diarrhea, or inflammation of intestines. Sensitivity to sunlight. Decreased production of sperm.

In part B and C M4344 will be administered with cytotoxic chemotherapy (carboplatin). There is extensive information on the side effect profiles of

this chemotherapeutic agent in human subjects with cancer which will be explained to the subjects. Based on the mechanism of action of M4344, the addition of M4344 to chemotherapy may increase the frequency and/or severity of these side effects.

Contacts

Public
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Subjects who meet all of the following inclusion criteria will be eligible for this study:
1. Male and female subjects *18 years of age
2. Disease status:
Part A2 and A3: Subjects with histologically or cytologically confirmed malignant advanced solid

tumors for which no standard therapy is available which may convey clinical benefit.
Part B: Subjects with 1 histologically or cytologically confirmed malignant advanced solid tumors for which no standard therapy is available which may convey clinical benefit, and/or subjects must have progressed after at least 1 prior chemotherapy regimen in the metastatic setting, and for which carboplatin would be considered standard of care.
Part C1, C2, and C3: Participants with 1 histologically or cytologically confirmed malignant advanced solid tumors for which no recommended standard therapy is available (i.e. participants who have exhausted all standard of care options according to NCCN Guidance) which may convey clinical benefit, and whose tumor has at least 1 of the following biomarkers as determined by a central trial assay or by an assay with appropriate regulatory status:
- C1 or C4: loss-of-function mutations in the gene ARID1A
- C2 or C5: loss-of-function mutations in the genes ATRX and/or DAXX
- C3 or C6: loss-of-function mutations in the gene ATM
3. Measurable disease according to RECIST criteria (Version 1.1)
4. WHO performance status of 0 or 1
5. Life expectancy of *12 weeks
6. Hematological and biochemical indices within the ranges shown below at Screening.
These values must be confirmed at the first day of dosing, before study drug administration:
a. Hemoglobin: *9.0 g/dL for Parts A and B; *8.0 g/dL and no blood transfusions in
the preceding 28 days for Part C
b. Absolute neutrophil count: *2.0 x 109/L
c. Platelet count: *125 x 109/L.
d. Serum bilirubin: *1.5 x upper limit of normal (ULN), except in the case of known
or suspected Gilbert*s syndrome.
e. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline
phosphatase (liver origin): *2.5 x ULN or *5 x ULN in presence of liver metastases
f. Serum albimin *2.5g/dL
g. Estimated glomerular filtration rate: *50 mL/min for Parts A and B; *40 mL/min
for Parts C
h. Prothrombin time: <1.25 x ULN
i. In addition, there should not be other clinically significant metabolic or hematologic abnormalities that are uncorrectable or that require ongoing, recurrent pharmacologic management.
7. Sign and date an informed consent document
8. Willing and able to comply with scheduled visits, treatment plan, lifestyle, laboratory

tests, contraceptive guidelines, and other study procedures

Exclusion criteria

Subjects who meet any of the following exclusion criteria are not eligible for this study:
1. Radiotherapy, unless brief course for palliative therapy, endocrine therapy, immunotherapy, or chemotherapy during the 4 weeks (6 weeks for nitrosoureas and Mitomycin-C, and 4 weeks for investigational medicinal products) or 4 drug half-lives
before first dose of study drug, whichever is greater
2. Part B1: More than 6 cycles of prior therapy with carboplatin, unless discussed with and
approved by the Merck medical monitor.
3. Ongoing toxic manifestations of previous treatments. Exceptions to this are alopecia or
certain Grade 1 toxicities, which in the opinion of the investigator should not exclude the
subject.
Part B1. Any known history of Grade 4 thrombocytopenia with any prior chemotherapy regimen (not applicable for Parts C)
4. Brain metastases unless asymptomatic, treated, stable, and not
requiring steroids for at least 4 weeks before first dose of study drug
5. Female subjects who are already pregnant or lactating, or plan to become pregnant within
6 months of the last dose of study drug are excluded. Female subjects of childbearing
potential must adhere to contraception guidelines as outlined in Section 11.7.5.1. Female
subjects will be considered to be of nonchildbearing potential if they have undergone
surgical hysterectomy or bilateral oophorectomy or have been amenorrheic for over
2 years with a screening serum follicle-stimulating hormone (FSH) level within the
laboratory*s reference range for postmenopausal females.
6. Male subjects with partners of childbearing potential must agree to adhere to contraception guidelines in Section 11.7.5.1. Men with pregnant or lactating partners or
partners who plan to become pregnant during the study or within 6 months of the last
dose of study drug are excluded.
7. Major surgery *4 weeks before first dose of study drug or incomplete recovery from a
prior major surgical procedure

8. Cardiac conditions as follows:
a. Clinically significant cardiovascular event within 6 months before study entry:
i. congestive heart failure requiring therapy
ii. unstable angina pectoris
iii. myocardial infarction
iv. Class II/III/IV cardiac disease (New York Heart Association)
v. presence of severe valvular heart disease
vi. presence of a ventricular arrhythmia requiring treatment
b. History of arrhythmia that is symptomatic or requires treatment (CTCAE Grade 2), symptomatic or uncontrolled atrial fibrillation despite treatment, or asymptomatic sustained ventricular tachycardia. Subjects with atrial fibrillation controlled by medication are permitted.
c. Uncontrolled hypertension (blood pressure *160/100 despite optimal therapy)
d. Second or third degree heart block with or without symptoms
e. QTc >470 msec (by either Fridericia*s or Bazett*s correction) not due to electrolyte abnormality and that does not resolve with correction of electrolytes
f. History of congenital long QT syndrome
g. History of torsades de pointes (or any concurrent medication with a known risk of inducing torsades de pointes)
h. Clinically-significant abnormality, including ejection fraction below normal institutional limits, present on transthoracic echocardiogram performed at Screening, for Parts A and B
9. Prior bone marrow transplant or extensive radiotherapy to greater than 15% of bone
marrow
10. Participation, or plan of participation, in another interventional clinical study while taking
part in this Phase 1 study of M4344. Participation in an observational study would be
acceptable
11. Any other condition which in the investigator*s opinion would not make the subject a
good candidate for the clinical study, including:
a. History of human immunodeficiency virus-1 (HIV-1), HIV-2, or unresolved hepatitis B or unresolved hepatitis C infection
b. High medical risk because of nonmalignant systemic disease including active uncontrolled infection
c. Subjects who have been diagnosed with Li-Fraumeni Syndrome or with ataxia telangiectasia
12. Part C only: Current malignancies of other types, with the exception of adequately treated
cone-biopsied in situ carcinoma of the cervix uteri and basal or squamous cell carcinoma
of the skin; prior cancer that has been in remission for at least 3 years would not be

excluded.
13. Current therapy:
a. Subjects receiving treatment with medications that are known to be strong inhibitors or inducers of cytochrome P450 3A4 (CYP3A4) that cannot be discontinued at least 1 week before first dose of study drug and for the duration of the study. Examples of strong CYP3A4 inhibitors or inducers are provided in Table 9-1.
b. Subjects receiving treatment with proton-pump inhibitors that cannot be discontinued at least 1 week before first dose of study drug and for the duration of the study. Examples of proton-pump inhibitors are provided in Table 9-1.
14. Subjects who cannot comply with restrictions for medications or food as specified in
Table 9-1

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):	05-05-2015
Enrollment:	16
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Carboplatin
Generic name:	NA
Registration:	Yes - NL intended use
Product type:	Medicine

Brand name:	Cisplatin
Generic name:	NA
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Gemcitabine
Generic name:	NA
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	11-12-2014
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-02-2015
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-11-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-11-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-10-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	01-11-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-03-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-09-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-10-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-11-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-03-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-03-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-04-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	08-01-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-03-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-07-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-07-2019
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:	05-12-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-04-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-06-2020

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-07-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-03-2021
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	EUCTREudraCT 2014-0-NL
ClinicalTrials.gov	NCT02278250
CCMO	NL51432.056.14