The AIM-HN and SEQ-HN Study: A 2 Cohort, Non-comparative, Pivotal Study Evaluating the Efficacy of Tipifarnib in Patients with Head and Neck Squamous Cell Carcinoma (HNSCC) with HRAS Mutations (AIM-HN) and the Impact of HRAS Mutations on Response to First Line Systemic Therapies for HNSCC (SEQ-HN)

Published: 28-01-2019
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Primary Objective: • To determine the objective response rate (ORR) of tipifarnib in subjects with Head and Neck Squamous Cell Carcinoma (HNSCC) with HRAS mutations with a VAF>=20% (High VAF population), as assessed by Independent Review Facility...

Ethical review	Approved WMO
Status	Completed
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON55489

Source
ToetsingOnline

Brief title
KO-TIP-007

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
Head and Neck Squamous Cell Carcinoma (HNSCC); Head and Neck Cancer

Research involving
Human

Sponsors and support

Primary sponsor: Kura Oncology, Inc.
Source(s) of monetary or material Support: Industry sponsored by the sponsor;Kura Oncology;Inc.

Intervention

Keyword: AIM-HN, HNSCC, SEQ-HN, Tipifarnib

Outcome measures

Primary outcome

The primary endpoint is the proportion of subjects with confirmed Objective

Response (OR), defined as either Complete Response (CR) or Partial Response

(PR), calculated using the mITT analysis set.

Secondary outcome

Secondary Endpoints

The following are secondary endpoints, evaluated in the AIM-HM part of the

study:

- Time to response

- Duration of response (DOR)

- Time to progression (TTP)

- Progression-free survival (PFS)

- 1-year progression-free rate and 1-year survival rate

- Overall survival rate (OS)

- Adverse Events

- Population PK parameters of tipifarnib

- Laboratory test results

- Vital Signs

- ECG results

Exploratory Endpoints

The following are exploratory endpoints, evaluated in the SEQ-HN part of the study:

- Proportion of HRAS mutations among subjects screened for the inclusion in the study

- Proportion of subjects with objective response to first line systemic therapy

- Progression free survival, duration of response, and overall survival

- Frequency and treatment outcomes (Objective response rate and survival-type endpoints) evaluated in subjects with identified other HNSCC generic alterations.

Study description

Background summary

This study investigates the Head-Neck-area Squamous Cell Carcinoma with a HRAS mutation. Head-neck cancer is a group of tumors that arise in the mouth, nose,

throat, the larynx, sinuses, or the salivary glands. Squamous cells form the surface of the skin and mucous membrane lining of hollow organs in the body and line the respiratory and digestive tracts. Tipifarnib is a drug that is currently being investigated and which is expected to block the proper functioning of proteins which are often abnormally active in cancer cells. Tipifarnib was tested on a number of trials with patients, including an ongoing phase 2 study. Based on the results observed, the sponsor has planned this pivotal study.

Study objective

Primary Objective:
• To determine the objective response rate (ORR) of tipifarnib in subjects with Head and Neck Squamous Cell Carcinoma (HNSCC) with HRAS mutations with a VAF>=20% (High VAF population), as assessed by Independent Review Facility (IRF).

Key Secondary Objectives:
• To determine the objective response rate (ORR) of tipifarnib in subjects with Head and Neck Squamous Cell Carcinoma (HNSCC) with HRAS mutations of any VAF (All VAF population), as assessed by IRF.
• To determine the Duration of Response (DOR) of tipifarnib in subjects with Head and Neck Squamous Cell Carcinoma (HNSCC) with HRAS mutations with a VAF>=20% (High VAF population), as assessed by IRF.
• To determine the Duration of Response (DOR) of tipifarnib in subjects with Head and Neck Squamous Cell Carcinoma (HNSCC) with HRAS mutations of any VAF (All VAF population), as assessed by IRF.

Other Secondary Objectives for AIM-HN:
• To determine the anti-tumor activity of tipifarnib in terms of progression free survival, and rate of progression free survival at 6 and 9 months in both the high VAF and all VAF populations
• To determine the anti-tumor activity of tipifarnib in terms of overall survival, and rate of overall survival at 12 months in both the high VAF and all VAF populations
• To determine the anti-tumor activity of tipifarnib in terms of time to response in both the high and all VAF populations
• To determine the anti-tumor activity of tipifarnib in terms of time to progression (TTP) in both the high and all VAF populations
• To investigate the safety and tolerability of tipifarnib according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI CTCAE v5.0).
• To investigate the effects of tipifarnib treatment on quality of life measures, including EORTC QLQ-H&N35 and EQ-5D-5L.
• To assess population pharmacokinetics (PK) of tipifarnib in subjects with HNSCC with HRAS mutations.

Other Secondary Objectives for SEQ-HN study and HRAS mutant population:
• To determine if HRAS mutational status is predictive of ORR on first line systemic treatment in patients with recurrent/metastatic HNSCC.
• To determine if treatment outcomes differ (PFS, DOR) with first line systemic therapy in patients with recurrent/metastatic HNSCC with and without HRAS mutations.
• To describe demographic characteristics in patients with HNSCC with and without HRAS mutations.
• To explore the frequency and treatment outcome interaction of other HNSCC genetic alterations.
• To identify trends in the data that may suggest relationships between covariates of interest and treatment outcome in patients with HNSCC with HRAS mutations.

Study design

KO-TIP-007 is an international, multicenter, open-label single- arm pivotal study. There are two sub-studies, not intended for comparison (1) an interventional open label, single arm, pivotal study evaluating the efficacy of tipifarnib in HRAS mutant HNSCC (AIM-HN) and (2) an observational study to evaluate the impact of HRAS mutations on response to first line systemic therapies for HNSCC (SEQ-HN).
AIM-HN, includes HNSCC subjects with HRAS mutations. AIM-HN subjects will receive treatment with tipifarnib and the outcome will address the primary objective of the KO-TIP-007 study. SEQ-HN, is an observational sub-study and includes wild type HRAS HNSCC subjects who consent to provide first line outcome data and additional follow up. HNSCC patients in whom HRAS mutations are identified and who meet eligibility criteria will be offered participation in AIM-HN. HNSCC patients in whom HRAS mutations are not identified may participate in SEQ-HN only. These patients will be followed and the comparison of outcomes of HRAS mutant and HRAS wild type HNSCC will address the exploratory objective to determine the effect of HRAS mutation on the ORR of first line systemic therapy in patients with recurrent/metastatic HNSCC, in order to explore preliminary data observations and literature that indicate HNSCC patients with HRAS mutations have poor prognosis with standard therapy (Ho 2017, Rampias 2014).
KO-TIP-007 will enroll a total of at least 305 subjects. AIM-HN, the tipifarnib treatment sub-study of KO-TIP-007, will investigate the efficacy of tipifarnib in at least 80 subjects with head and neck tumors of confirmed squamous histology with HRAS mutations. SEQ-HN, the non-interventional observational sub-study, will enroll an additional, at least 225 subjects with HRAS wildtype HNSCC tumors. Additional HRAS mutant subjects that consent to pre-screening, but do not enroll in AIM-HN may have first line treatment data collected as well.

Intervention

please refer to section B6.

Study burden and risks

please refer to section E9.

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

Inclusion criteria: AIM-HN
For inclusion of a subject in the tipifarnib treatment portion of the study (AIM-HN), all of the following inclusion criteria must be fulfilled. If a subject does initially not meet any inclusion criteria, the subject may be

re-screened at a later time:
1. At least 18 years of age.
2. Histologically confirmed head and neck cancer (oral cavity, pharynx, larynx, sinonasal, nasopharyngeal, or unknown primary) of squamous histology not amenable to local therapy with curative intent (surgery or radiation therapy with or without chemotherapy). Enrollment may proceed with local diagnosis but all subjects must consent to provide tumor tissue for a central pathology review.
3. Documented treatment failure from most recent prior therapy (e.g. tumor progression, clinical deterioration, or recurrence), and from at least one prior platinum-containing regimen, in any treatment setting. The most recent prior and platinum-based therapy may be the same regimen. Those subjects who, at the judgment of the investigator, are considered clinically unsuitable to receive standard platinum-containing regimen, may also be enrolled and the reason for clinical unsuitability recorded. There is no limit on the number of prior lines of therapy.
4. Known tumor missense HRAS mutation detected by Next Generation Sequencing (NGS) or any other methodology approved by the Sponsor. Variant allele frequency (VAF) needs to be determined and must be available. HRAS status should be assessed on tumor tissue obtained subsequent to the most recent prior therapy so that the most accurate tumor biology is evaluated. If tumor tissue that does not meet this criterion must be used (e.g. risk of new biopsy is too high, patient refuses new biopsy), the investigator should document the reason. Enrollment may proceed with the identification of a missense HRAS mutation using a test preferred by the investigator and approved by the Sponsor during pre-screening, but all subjects must consent to provide tumor tissue for central HRAS confirmation.
a) At least 59 per protocol subjects must have a VAF >=20%
b) No more than approximately 21 per protocol subjects may have a VAF of <20%
5. Measurable disease by RECIST v1.1 (Appendix I) that meets the criteria for selection as a target lesion according to RECIST v1.1. The presence of at least one measurable target lesion per RECIST v1.1 must be confirmed by local radiology prior to subject entry.
6. At least 2 weeks or 5 half-lives, whichever is longer, since the last systemic therapy regimen prior to Cycle 1 Day 1. Last dose of any prior checkpoint inhibitor therapy must have been administered at least 2 weeks prior to C1D1. Subjects must have recovered to NCI CTCAE v5.0 < Grade 2 from all acute toxicities (excluding Grade 2 toxicities that are not considered a safety risk by the Sponsor and Investigator) or toxicity must be deemed irreversible by the Investigator.
7. At least 2 weeks since last radiotherapy. Subjects must have recovered from all acute toxicities from radiotherapy.
8. ECOG performance status of 0-1.
9. Acceptable liver function:
a) Bilirubin < 1.5 times upper limit of normal (x ULN).
b) AST (SGOT) and ALT (SGPT) < 1.5 x ULN.
The subject must meet/continue to meet these criteria at the time of first

dosing, as confirmed by analysis within 72 hours of C1D1.
10. Acceptable renal function with either serum creatinine < 1.5 x ULN or a calculated creatinine clearance >= 60 mL/min using the Cockcroft-Gault or Modification of Diet in Renal Disease (MDRD) formulas.
The subject must meet/continue to meet these criteria at the time of first dosing, as confirmed by review of analysis performed within 72 hours of C1D1.
11. Acceptable hematologic status:
a) ANC > 1000 cells/µL.
b) Platelet count > 75,000/µL.
c) Hemoglobin > 8.0 g/dL.
The subject must meet/continue to meet these criteria at the time of first dosing, as confirmed by review of analysis performed within 72 hours of C1D1.
12. Female subjects must be:
a) Of non-child-bearing potential (surgically sterilized or at least 2 years post-menopausal); or
b) If of child-bearing potential, subject must use a highly effective method of contraception, such as combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation, progestogen-only hormonal contraception associated with inhibition of ovulation, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomised partner or sexual abstinence. Both females and male subjects with female partners of child-bearing potential must agree to use a highly effective method of contraception from the first dose of tipifarnib, during tipifarnib treatment, and at least 28 days after last dose of tipifarnib for females and 90 days for males. Female subjects must have a negative serum or urine pregnancy test within 72 hours prior to start of trial medication.
c) Not breast feeding at any time during the study.
13. Written and voluntary informed consent understood, signed and dated.

Inclusion Criteria: SEQ-HN
For inclusion of a subject in the noninterventional portion of the study (SEQ-HN), all of the following inclusion criteria must be fulfilled:
1. At least 18 years of age.
2. Histologically confirmed head and neck cancer (oral cavity, pharynx, larynx, sinonasal, nasopharyngeal, or unknown primary) of squamous histology.
3. HRAS wildtype (i.e. have no identified tumor missense HRAS mutation) determined by a test preferred by the investigator and approved by the Sponsor or through central HRAS testing.
4. Will or has received at least one systemic anti-cancer therapy for recurrent or metastatic HNSCC for which there is available outcome information in terms of ORR, or can be determined based on the subject*s records. Subjects who have not yet received or completed at least one systemic anti-cancer therapy for recurrent or metastatic HNSCC must consent to the collection of treatment outcome information and additional follow up contact in order to participate in the SEQ-HN portion of the study.
5. Written and voluntary informed consent understood, signed and dated.

Exclusion criteria

Inclusiecriteria: AIM-HN
If a subject initially meets any exclusion criteria, the subject may be re-screened at a later time.
1. Has disease that is suitable for local therapy administered with curative intent.
2. Histologically confirmed salivary gland, thyroid, (primary) cutaneous squamous or nonsquamous histologies (e.g. mucosal melanoma).
3. Known additional malignancy that is progressing or requires active treatment (excluding non-melanoma skin cancer, adjuvant hormonal therapy for breast cancer and hormonal treatment for castration sensitive prostate cancer).
4. Ongoing treatment with an anticancer agent not contemplated in this protocol (excluding adjuvant hormonal therapy for breast cancer and hormonal treatment for castration sensitive prostate cancer).
5. Prior treatment (at least 1 full treatment cycle) with a farnesyltransferase inhibitor (FTI).
6. Any use of investigational therapy within 2 weeks of Cycle 1 Day 1 (C1D1) or 5 half-lives (whichever is longer). Last dose of any prior checkpoint inhibitor therapy must have been administered at least 2 weeks prior to C1D1.
7. Received treatment for unstable angina within prior year, myocardial infarction within the prior year, cerebro-vascular attack within the prior year, history of New York Heart Association grade III or greater congestive heart failure, or current serious cardiac arrhythmia requiring medication except atrial fibrillation.
8. Non-tolerable Grade 2 or >= Grade 3 neuropathy or evidence of unstable neurological symptoms within 4 weeks of Cycle 1 Day 1. Non-tolerable Grade 2 toxicities are defined as those with moderate symptoms that the subject is not able to endure for the conduct of instrumental activities of daily life or that persists >= 7 days.
9. Major surgery, other than diagnostic surgery, within 2 weeks prior to Cycle 1 Day 1, without complete recovery.
10. Active, uncontrolled bacterial, viral, or fungal infections requiring systemic therapy, including known history of infection with human immunodeficiency virus or an active infection with hepatitis B or hepatitis C.
11. Subjects who have exhibited allergic reactions to tipifarnib or structural compounds similar to tipifarnib or to its excipients. This includes hypersensitivity to imidazoles, such as clotrimazole, ketoconazole, miconazole and others in this drug class. Subjects with hypersensitivity to these agents will be excluded from enrollment.
12. Required use of concomitant medications classified as strong inhibitors or inducers of cytochrome P450 3A4 (CYP3A4) or UDP-glucuronosyltransferase (UGT).
13. Concomitant disease or condition that could interfere with the conduct of the study or that would, in the opinion of the investigator, pose an unacceptable risk to the subject in this study.
14. Female subjects who are pregnant or lactating.

15. Unwillingness or inability to comply with the study protocol for any reason.

Exclusion Criteria: SEQ-HN
1. Histologically confirmed salivary gland, thyroid, (primary) cutaneous squamous or nonsquamous histologies (e.g. mucosal melanoma).
2. Concomitant disease or condition that could interfere with the conduct of the study or that would, in the opinion of the investigator, pose an unacceptable risk to the subject in this study.
3. The subject has legal incapacity or limited legal capacity.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	07-10-2019
Enrollment:	35
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Tipifarnib
Generic name:	n.a.

Ethics review

Approved WMO

Date:	28-01-2019

Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-06-2019
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	02-10-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-10-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-09-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-10-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	02-06-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-10-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-11-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	31-01-2022

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	13-08-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	29-09-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2018-001437-40-NL
ClinicalTrials.gov	NCT03719690
CCMO	NL67091.042.19

Study results

Date completed:	15-02-2023
Results posted:	16-10-2023

First publication
07-09-2023