A Phase 1/1b Open-Label, Multicenter, to Investigate the Safety, Tolerability, Pharmacokinetics, and Antitumor Activity of KIN 2787 in Participants with BRAF and/or NRAS Mutation positive Solid Tumors

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Part A1(KIN-2787 Monotherapy Escalation):Determine safety and tolerability of PO administration of Kin-2787 including DLT in participants with BRAFmutation-positive advanced or metastatic solid tumors or melanoma harboring NRAS-mutation. Identify...

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

Summary

ID

NL-OMON56188

Source
ToetsingOnline

Brief title
KIN-2787Activity in Participants with BRAF/NRASMutation PositiveSolidTumors

Condition

- Other condition
- Skin neoplasms malignant and unspecified

Synonym
advanced tumors, Solid tumors

Health condition

Any unresectable and locally advanced or metastatic solid tumors

Research involving

Human

Sponsors and support

Primary sponsor: Kinnate Biopharma
Source(s) of monetary or material Support: Sponsor is Kinnate Biopharma;Inc.

Intervention

Keyword: - Advanced solid tumors, - BRAF en/of NRAS mutation, - Melanoma, - Non-small cell lung cancer

Outcome measures

Primary outcome

Safety endpoints include the following:

• Incidence of dose limiting toxicity (DLTs),

• Incidence of treatment-emergent adverse events (TEAEs), treatmentrelated

AEs

• Clinically significant changes in vital signs, physical examinations,

ECGs, and clinical laboratory tests

Efficacy (as assessed by the Investigator) will be measured by the

following:

• Objective response rate (ORR) defined as the rate of partial responses

(PR) plus

complete responses (CR) according to RECIST v1.1

• Disease control rate (DCR)

• Duration of overall response (DOR)

• Duration of stable disease

Secondary outcome

PK parameters of KIN-2787 and KIN-2787 + binimetinib including, but

not limited to, maximum observed plasma concentration (Cmax), time to achieve Cmax (tmax), and area under the plasma concentration-time curve (AUC), including in the fed and fasted states.

Exploratory Endpoints:

• KIN-2787 and KIN-2787 + binimetinib exposure/safety and exposure/efficacy relationships

• Characterization of potential metabolites of KIN-2787 in plasma and urine

• Progression-free survival (PFS), and overall survival (OS)

• Biomarker quantification by biochemical and/or genetic analysis of blood and/or tumor samples including, but not limited to the pharmacodynamic effect on pERK, DUSP6 RNA and proliferation marker, Ki-67.

• Changes in ctDNA concentration and mutational profiles

• Potential biomarkers by biochemical and/or genetic analysis of blood and/or tumor samples

• Population PK analysis

• Objective response evaluation of previously untreated brain metastases as assessed by Response Assessment in Neuro-Oncology

Brain Metastases (RANO-BM) by the Investigator.

• Patient reported outcomes (Part B only)

• Evaluation of PK of new tablet formulation (US only)

Study description

Background summary

Initially, Kinnate began development of KIN-2787 for the treatment of patients with melanoma and NSCLC subpopulations with tumors harboring Class II or III BRAF mutations that include specific BRAF point mutations (other than BRAF V600E), BRAF insertions/deletions (indels), and
BRAF gene fusion events. These patients are not eligible to receive current BRAF-targeted therapies, typically do not harbor other oncogenic driver genes for which targeted therapies are available and have few other treatment options. Additionally, NSCLC patients and melanoma patients with BRAF Class II and III mutations have poor prognoses, represent cancer indications of high need, and will be the primary cancer populations enrolled in Study KN-8701. Patients with advanced or metastatic NSCLC, melanoma, CRC, and thyroid cancer with BRAF Class I mutations are eligible to receive approved BRAF-targeted therapies. These RAF inhibitor drugs are often used in combination with a MEK inhibitor, and together provide significant clinical benefit. However, due to the frequent emergence of acquired resistance in many of these patients, and the fact that other solid tumors driven by Class I, II, or III BRAF mutations are not eligible for approved BRAF-directed therapies, an unmet need persists to develop next generation BRAF-targeted therapies. Collectively, these patients will also be evaluated in Study KN-8701.

Study objective

Part A1(KIN-2787 Monotherapy Escalation):Determine safety and tolerability of PO administration of Kin-2787 including DLT in participants with BRAF mutation-positive advanced or metastatic solid tumors or melanoma harboring NRAS-mutation.
Identify MTD and/or appropriate dose for Part B1

Part A2 (KIN-2787+Binimetinib Escalation):Determine safety and tolerability of PO administration including DLTs in participants with
oncogenic BRAF or NRAS mutation-positive advanced or metastatic solid tumors.
Identify MTD and/or 1or 2 RP2D for further clinical
investigation

PartB1(KIN-2787 Monotherapy Expansion):Assess preliminary evidence of anti-cancer activity of KIN-2787 in participants with advanced or metastatic solid cancers that harbor any oncogenic BRAF genomic alteration

PartB2(KIN-2787+Binimetinib Expansion):evaluate preliminary evidence of anti-cancer activity of KIN-2787 + binimetinib for tumors with NRAS Q61, G12, and G13 + and oncogenic BRAF Class II mutations for 1 or more RP2D based on the results of Part A 2.

Study design

The study consists of Part A Dose Escalation and Part B Dose Expansion, both of which include
assessment of KIN-2787 monotherapy (Parts A1 and B1) and KIN-2787 + binimetinib combination therapy (Parts A2 and B2).
Part A (Dose Escalation):
Part A1 will evaluate the safety, tolerability, PK, and pharmacodynamics (PD) of KIN-2787 in
participants with BRAF mutation-positive advanced or metastatic solid tumors and/or melanoma harboring an NRAS mutation. Part A1 will use an accelerated titration design (single-participant dose levels) followed by a traditional 3 + 3 dose-escalation scheme to identify the MTD and/or
RP2D of KIN-2787. The MTD is defined as the maximum daily oral dose at which < 33% of participants experience a DLT during the 28-day DLT evaluation period.
KIN-2787 will be administered as an oral dose twice daily (BID) every day for 28 days in 28-day treatment cycles.
The starting dose, Dose Level (DL) 1, will be 50 mg per day (administered as 25 mg BID), and
dose escalation increments will follow a modified Fibonacci sequence. The planned KIN-2787 dose levels are indicated in the protocol.
An accelerated titration dose escalation design principle will be employed in which 1 participant per cohort will be evaluated until evidence of biologic activity is observed. At which time, that cohort will be expanded by 2 participants. This and all subsequent dose level cohorts will
proceed using the 3 + 3 dose escalation design. For purposes of the above discussion,
either (1) a DLT or (2) at least 1 Grade 2 adverse event (AE) not clearly attributable to underlying disease or extraneous cause (excluding
Grade 2 Laboratory Investigation AEs deemed non-clinically significant by the Investigator).
Starting with DL3, the KIN-2787 dose will be escalated using a traditional 3 + 3 study design and will continue until stopping rules are met, or until the MTD or the dose at which the anticipated maximal pharmacologic activity (informed by PK and PD biomarkers) is achieved.
With this 3 + 3 design, at least 3 participants will be enrolled into each dose level from DL3 onwards. If none of the 3 participants in a dose level experiences a DLT within the DLT period (28 days from the first dose of

KIN-2787 for all dose levels), another 3 participants will be treated at the next higher dose level. No additional participants will be treated at a given dose level if 2 or more of the participants in that dose level develop a DLT in Cycle 1.

For the first 2 participants who receive KIN-2787 at a specified dose level, there will be at least 24 hours between the first dose of KIN-2787 in the first and second participants.

Dose escalation will continue until the highest planned dose level is determined to be safe and tolerable with a minimum of 6 DLT-evaluable participants at that dose level (i.e., the dose level considered to be the RP2D), or until MTD is reached. Up to approximately 26 participants will be required to estimate the MTD and/or the RP2D.

The Dose Review Committee (DRC) consisting of Investigators and Sponsor representatives will review all available safety, PK, and PD data prior to initiating enrollment at the next dose level. The DRC will review the safety and tolerability of each dose level of KIN-2787 monotherapy after participants at that particular dose level have completed at least 1 full cycle.

Part A will continue until stopping rules are met or until the MTD or the dose where the anticipated maximal pharmacologic activity (e.g., RP2D) is achieved. The DRC will also evaluate all available safety data and PK/PD data to determine the RP2D for Part B.

The effect of food on the PK of KIN-2787 will be evaluated in at least 6 participants during Part A1 at DL3, DL4, and DL5 using a randomized crossover design.

Participants who are receiving KIN-2787 monotherapy in Part A1 will have the opportunity to crossover to combination therapy (Part A2) with KN-2787 + binimetinib if they meet the criteria specified in the protocol.

Part A2 will not be initiated until preliminary proof of mechanism (PPOM) clinical criteria have been met in the monotherapy dose escalation cohorts. At the end of each Part A1 dose level cohort, the DRC will determine if the criteria for PPOM have been met and will recommend if Part A2 should be initiated.

Part A2 will include participants with pretreated BRAF Class I, BRAF Class II, BRAF Class III, or NRAS mutated solid tumors. Emerging clinical data will be used to monitor and update the prioritization for enrollment of each mutation type throughout the study. For KIN-2787, the starting dose will be 1 dose level below the dose level that met PPOM criteria or 1 dose level below the dose level considered safe at the discretion of the DRC. For binimetinib, the starting dose will be the labeled, approved dose of 45 mg BID. KIN-2787 and binimetinib will be administered together as an oral dose every day in 28-day treatment cycles.

Dose escalation for the combination dose levels will follow a 3 +3 design. Combination dose levels may be assessed in parallel. The DRC will recommend subsequent combination dose levels based on available safety, tolerability, and PK data from the previous dose levels.

Intra-participant dose escalations and backfill are allowed in Part A at the discretion of the Investigator and after consultation with the Sponsor. The

backfill dose level(s) for KIN-2787 monotherapy and for KIN-2787 combination with binimetinib will be the most recent dose(s) that have been cleared by the DRC and are regarded as safe and tolerable. Intra-participant dose escalation may only be considered if the participant meets all protocol-specified criteria.
Part B (Dose Expansion):
Part B1 monotherapy dose expansion part of the study can begin once the KIN-2787 monotherapy MTD and/or RP2D has been determined in Part A1. Part B1 will evaluate the anti-tumor activity of KIN-2787 monotherapy at the RP2D in the following cohorts:
Cohort 1: Participants with unresectable and locally advanced (American Joint Committee on Cancer [AJCC] Stage III) or metastatic (AJCC Stage IV) non-small cell lung cancer (NSCLC) with any BRAF Class II mutation.
Cohort 2: Participants with unresectable and locally advanced (AJCC Stage III) or metastatic (AJCC Stage IV) NSCLC with any BRAF Class III or other BRAF non-Class I mutation.
Cohort 3: Participants with unresectable and locally advanced (AJCC Stage III) or metastatic (AJCC Stage IV) melanoma with any BRAF Class II mutation
Cohort 4: Participants with unresectable and locally advanced (AJCC Stage III) or metastatic (AJCC Stage IV) melanoma with any BRAF Class III or other BRAF non-Class I mutation.
Cohort 5: Participants with any unresectable and locally advanced (AJCC Stage III, or comparable Stage with other staging systems) or metastatic (AJCC Stage IV) solid tumor (other than NSCLC or melanoma) with any BRAF Class II mutation
Cohort 6: Participants with any unresectable and locally advanced (AJCC Stage III, or comparable Stage with other staging systems) or metastatic (AJCC Stage IV) solid tumor (other than NSCLC or melanoma) with any BRAF Class III or other BRAF non--Class I mutation.
Cohort 7: Participants with any unresectable and locally advanced (AJCC Stage III, or comparable Stage with other staging systems) or metastatic (AJCC Stage IV) solid tumor with any BRAF Class I oncogenic mutation.
Enrollment of participants in the Dose Expansion cohorts will occur concurrently. The eligibility of participants with certain genetic alterations may be restricted to ensure appropriate genotype representation. In addition, in Cohorts 5-7, tumor types will be monitored to ensure a broad representation of various solid tumors.
In the United States (US) only for all Part B1 cohorts, comparison of the PK of a new KIN-2787 formulation more suited for commercial manufacture will be evaluated in approximately 6 participants randomized to the 2 formulations in a 1:1 fashion starting at C1D1.
Part B2, combination Dose Expansion part of the study, can begin once the MTD and/or the RP2D of KIN-2787 + binimetinib have been identified. Part B2 will evaluate the anti-tumor activity of KIN-2787 in combination with binimetinib for 2 cohorts: Cohort 1 for participants with
NRAS mutation solid tumors, including melanoma, and Cohort 2 for participants with BRAF Class II mutation solid tumors. One or more RP2D may be assessed within each cohort.
Enrollment into the NRAS and BRAF Class II mutation groups may or may not occur

concurrently depending on the evolving clinical data. Participants' tumor genetic alterations and various tumor types will be monitored to ensure broad representation within each cohort.
For both Part B1 and Part B2, a Data Monitoring Committee (DMC) will review all available safety, tolerability, and treatment efficacy for all cohorts throughout the duration of the study.
The DMC will recommend continuation or termination of any cohort or even the study based on the evaluation of the results. A Bayesian efficacy modeling will be used to conduct continuous monitoring assessment on efficacy data to evaluate futility.

Intervention

See detailed description in section Study design

Study burden and risks

Please refer to section E.9

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

Key inclusion criteria include the following:
General Considerations:
1. Adult participants (>= 18 years of age) with histologically or cytologically confirmed diagnosis of metastatic or advanced-stage malignancy will be eligible for this study.
2. Participants with brain metastasis that are asymptomatic and do not require treatment in the opinion of the investigator.
3. Participants will provide archived tumor tissue specimen (formalinfixed paraffin-embedded [FFPE] specimen) obtained within the last 5 years (if available), and will undergo mandatory pre-treatment
tumor biopsy, if medically feasible.
4. A participant's tumor must harbor an oncogenic BRAF Class I, II, or III mutation or be melanoma with an NRAS Q61, G12, or G13 positive mutation identified by previous genomic analysis of tumor tissue or ctDNA conducted in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory (in United States
[US]) or in accordance with local regulatory requirements (in other countries).
Study Part Specific Considerations - Part A1:
1. Participants with any type of advanced or metastatic solid tumor with oncogenic BRAF Class I, Class II or Class III mutations and NRASmut positive melanoma.
2, Participants must have received prior standard therapy appropriate for their tumor type and stage of disease, or in the opinion of the Investigator, would be unlikely to tolerate or derive clinically meaningful benefit from appropriate standard of care therapy.
3. However, participants may enroll without having been pretreated with a small molecule BRAF-, MEK-, or MAPK-directed inhibitor therapy if such treatment has not been approved for that indication.
Study Part Specific Considerations - Part A2:
1. Participants with NRAS Q61, G12, or G13 positive mutated advanced solid tumors and oncogenic BRAF pretreated Class I, II or III mutated advanced solid tumors
2. Participants should have previously received an approved BRAF inhibitor (with or without an approved MEK inhibitor), if authorized and available unless, in the opinion of the Investigator, the participant would be unlikely to tolerate or derive clinically meaningful benefit from that treatment.

Study Part Specific Considerations - Part B1:
1. Participants with unresectable and locally advanced or metastatic NSCLC, melanoma, or any other unresectable and locally advanced solid tumor with oncogenic BRAF Class I, II, or III mutations
Study Part Specific Considerations - Part B2:
1. Participants with advanced or metastatic solid cancers harboring the NRAS Q61, G12, or G13 mutations or any oncogenic BRAF Class II mutations.
2. Participants must have received prior standard therapy appropriate for their tumor type and stage of disease, or in the opinion of the Investigator, would be unlikely to tolerate or derive clinically meaningful benefit from appropriate standard of care therapy.

Exclusion criteria

Key exclusion criteria include the following:
. Participants may not have any unresolved toxicities from prior antitumor therapy or significant concomitant diseases.
2. In Part B1 and B2, previous treatment with any approved or in-development small molecule BRAF-, MEK-, or MAPK-directed inhibitor therapy is excluded.

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):	10-11-2022
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	KIN-2787
Generic name:	KIN-2787
Product type:	Medicine
Brand name:	Mektovi
Generic name:	Binimetinib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	19-04-2022
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	19-07-2022
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	26-10-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-04-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-06-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-08-2023
Application type:	Amendment
Review commission:	METC NedMec

Approved WMO Date:	01-09-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	07-11-2023
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	EUCTR2021-005389-16-NL
ClinicalTrials.gov	NCT04913285
CCMO	NL79729.031.22