A PHASE Ia/Ib DOSE-ESCALATION AND DOSE EXPANSION STUDY EVALUATING THE SAFETY, PHARMACOKINETICS, AND ACTIVITY OF GDC-6036 AS A SINGLE AGENT AND IN COMBINATION WITH OTHER ANTI-CANCER THERAPIES IN PATIENTS WITH ADVANCED OR METASTATIC SOLID TUMORS WITH A KRAS G12C MUTATION

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This study has been transitioned to CTIS with ID 2023-506311-18-00 check the CTIS register for the current data. This Phase Ia/Ib study will evaluate the safety, pharmacokinetics, immunogenicity (as applicable for study biotherapeutics), preliminary...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Malignant and unspecified neoplasms gastrointestinal NEC
Study type	Interventional

Summary

ID

NL-OMON56305

Source
ToetsingOnline

Brief title
GO42144

Condition

- Malignant and unspecified neoplasms gastrointestinal NEC
- Miscellaneous and site unspecified neoplasms malignant and unspecified
- Respiratory tract neoplasms

Synonym
Locally Advanced or Metastatic Solid Tumors; locally advanced or tumors that metastasized

Research involving
Human

Sponsors and support

Primary sponsor: Genentech Inc. (een lid van de Roche groep)
Source(s) of monetary or material Support: Farmaceutisch bedrijf.

Intervention

Keyword: GDC-6036, KRAS G12C gene mutation, phase Ia/Ib, Solid tumors

Outcome measures

Primary outcome

• Incidence and severity of adverse events, with severity determined according

to National Cancer Institute Common Terminology Criteria for Adverse Events,

Version 5.0 (NCI CTCAE v5.0)

• Incidence and nature of dose-limiting toxicities (DLTs)

• Change from baseline in targeted vital signs

• Change from baseline in targeted clinical laboratory test results

• Change from baseline in targeted ECG parameters

Secondary outcome

Pharmacokinetic endpoints:

• Plasma concentrations of GDC-6036 and erlotinib at specified timepoints

• Serum concentrations of atezolizumab, cetuximab, and bevacizumab at specified

timepoints

Immunogenicity endpoints:

• Incidence of anti-drug antibodies (ADAs) to each study biotherapeutic (atezolizumab, cetuximab, and bevacizumab) during the study relative to the prevalence of ADAs at baseline

• Correlation between ADA status for each study biotherapeutic and efficacy, safety, and PK endpoints

Activity endpoints:

• Objective response rate (ORR), defined as the proportion of patients with a complete response (CR) or partial response (PR) on two consecutive occasions >= 4 weeks apart, as determined by the investigator according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

• Duration of response (DOR), defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause during the study (whichever occurs first), as determined by the investigator according to RECIST v1.1

• Progression-free survival (PFS), defined as the time from first treatment at Cycle 1 Day 1 to the first occurrence of disease progression or death from any cause during the study (whichever occurs first), as determined by the investigator according to RECIST v1.1

Biomarker endpoint:

• Relationship between exploratory biomarkers in blood, plasma, and tumor

tissue and safety, PK, activity, or other biomarker endpoints

Additional endpoints:

• Relationship between GDC-6036 exposure (PK parameters) and safety and

activity endpoints

• Relationship between tumor pharmacodynamic effects of GDC-6036 and safety and

activity endpoints

Study description

Background summary

The Kirsten rat sarcoma viral oncogene homolog (KRAS) is a central component of the RAS/MAPK signal transduction pathway, an intracellular network of proteins that transmit extracellular growth factor signals to regulate cell proliferation, differentiation, and survival. Mutations in KRAS can result in alterations at several amino acids, including glycine 12 (G12), glycine 13, and glutamine 61, commonly found in solid tumors and associated with tumorigenesis and aggressive tumor growth (Der et al. 1982; Parada et al. 1982; Santos et al. 1982; Taparowsky et al. 1982; Capon et al. 1983). Oncogenic KRAS mutations that result in the change from G12 to cysteine (G12C) are prevalent in non-small cell lung cancer (NSCLC) (~12%), colorectal cancer (CRC) (~4%), and other tumor types (~4%) (Bailey et al. 2016; Campbell et al. 2016; Giannakis et al. 2016; Hartmaier et al. 2017; Jordan et al. 2017).

Advanced stage tumors harboring the KRAS G12C mutation (hereafter referred to as KRAS G12C-positive tumors), including NSCLC, CRC, and other solid tumors, are incurable and carry a poor prognosis (Roman et al. 2018; Wan et al. 2019). In addition, patients with advanced stage KRAS G12C*positive cancers may derive limited benefit from select chemotherapies and targeted therapies, thus, restricting effective available treatment options (Roman et al. 2018).

Initial systemic treatment options for advanced stage or metastatic NSCLC (without known oncogenic drivers that have available targeted therapies) include PD-1/PD-L1 inhibitors with or without chemotherapy (Gong et al. 2018). Subsequent treatment options may include platinum-containing chemotherapy

combinations followed by single-agent chemotherapy with limited duration of disease control (NCCN 2020a). Although a minority of patients achieve long-term disease control, in general, advanced stage or metastatic NSCLC remains an incurable disease. Recent data suggest that KRAS mutation status may be associated with response to single-agent PD-1 inhibitor therapy and that chemotherapy plus a PD-1 inhibitor may be effective regardless of KRAS mutation status (Gadgeel et al. 2019; Herbst et al. 2019).

For advanced or metastatic CRC, systemic treatment can consist of combinations of active agents or select individual agents and includes 5-fluorouracil/leucovorin, capecitabine, irinotecan, oxaliplatin, bevacizumab, cetuximab, panitumumab, ziv-aflibercept, ramucirumab, regorafenib, trifluridine-tipiracil, pembrolizumab, nivolumab, ipilimumab, and encorafenib. Treatment is selected based on the goals of care, type and timing of prior therapy, mutational profile of the tumor, anticipated toxicity profile, and patient*s performance status (NCCN 2020b). Specifically, KRAS mutations were associated with resistance to anti-EGFR therapies (Lièvre et al. 2006; Karapetis et al. 2008; Van Cutsem et al. 2009; Misale et al. 2012). Thus, patients whose cancers harbor KRAS mutations are not eligible for treatment with cetuximab or panitumumab (NCCN 2020b) and treatment options remain limited.

Other tumor types with the KRAS G12C mutation include cancers of the pancreas, breast, ovary, endometrium, and appendix, as well as gastric cancer and myeloma (Hartmaier et al. 2017). Treatment is based on tumor type as well as patient*s performance status, goals of care, and prior therapy. However, because the prevalence of KRAS G12C-positive tumors is low, there is no specific guidance on treatment or management.
Although previously considered an *undruggable* cancer target, the landmark discovery of the switch II pocket within KRAS has enabled the development of covalent inhibitors specific for KRAS G12C (Ostrem et al. 2013). The clinical development of covalent inhibitors of KRAS G12C offers a potential therapeutic intervention to prevent or delay the progression of cancers that harbor a KRAS G12C mutation (McCormick 2019). Early clinical data from covalent inhibitors specific for KRAS G12C demonstrate single-agent anti-tumor activity and potential to improve treatment options and outcomes for patients with advanced stage cancer that harbors the KRAS G12C mutation (Jänne et al. 2019; Hong et al. 2020).

The investigational medicinal products (IMPs) for this study are GDC-6036, atezolizumab, cetuximab, bevacizumab, and erlotinib.
GDC-6036 is an oral, covalent, anti-cancer therapeutic agent that selectively inhibits KRAS G12C, but not other mutations in KRAS, the wild-type form of KRAS, or other members of the RAS family. Nonclinical studies demonstrate that treatment of KRAS G12C-positive cancer cell lines or tumor xenograft models with GDC-6036 results in decreased KRAS pathway signaling, suppression of proliferation, and induction of apoptosis. Results from nonclinical toxicity

and safety pharmacology studies completed to date characterize the toxicology profile of GDC-6036 and support the administration of GDC 6036 to patients with advanced cancer. Toxicities observed in nonclinical species are expected to be manageable and/or monitorable in a clinical setting. Refer to the GDC-6036 Investigator's Brochure for details on nonclinical studies.

Atezolizumab is a humanized IgG1 monoclonal antibody that targets PD L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Atezolizumab shows anti tumor activity in both nonclinical models and cancer patients and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy.

Cetuximab is a chimeric monoclonal IgG1 antibody that is specifically directed against the epidermal growth factor receptor (EGFR, also known as HER1 or c-ErbB-1). Cetuximab binds specifically to the EGFR on both normal and tumor cells and competitively inhibits the binding of epidermal growth factor (EGF) and other ligands, such as transforming growth factor-alpha.

Bevacizumab is a recombinant humanized monoclonal antibody that is specifically directed against vascular endothelial growth factor (VEGF) that recognizes all isoforms of VEGF. It may exert a direct anti-angiogenic effect by binding to and clearing VEGF from the tumor environment.

Erlotinib is an orally active, potent, selective inhibitor of the EGFR tyrosine kinase. EGFR is expressed on the cell surface of both normal and cancer cells. Erlotinib binding affinity for EGFR exon 19 deletion or exon 21 (L858R) mutations is higher than its affinity for the wild-type receptor. In nonclinical models, inhibition of EGFR autophosphorylation results in cell stasis and/or death.

Atezolizumab, cetuximab, bevacizumab, and erlotinib are approved (as single agent and/or in combination with other anti-cancer therapies) for the treatment of different types of carcinomas.

Study objective

This study has been transitioned to CTIS with ID 2023-506311-18-00 check the CTIS register for the current data.

This Phase Ia/Ib study will evaluate the safety, pharmacokinetics, immunogenicity (as applicable for study biotherapeutics), preliminary activity, and biomarkers of GDC-6036 as a single agent (Arm A) and in combination with other anti-cancer therapies in patients with advanced or metastatic solid tumors with a KRAS G12C mutation. Combination therapies will include

atezolizumab (Arm B), cetuximab (Arm C), bevacizumab (Arm D), and erlotinib (Arm E) in NSCLC, CRC, and other solid tumors. Specific objectives and corresponding endpoints for the study are outlined below.

Safety Objective (Primary Study Objective)
The safety objective for this study is to evaluate the safety of GDC-6036 as a single agent and in combination with other anti-cancer therapies on the basis of the following endpoints:
• Incidence and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0)
• Incidence and nature of dose-limiting toxicities (DLTs)
• Change from baseline in targeted vital signs
• Change from baseline in targeted clinical laboratory test results
• Change from baseline in targeted ECG parameters

Pharmacokinetic Objectives
The pharmacokinetic (PK) objectives for this study are to characterize the PK profile of GDC 6036 when administered as a single agent and in combination with other anti cancer therapies and to characterize the PK profile of these anti-cancer therapies when administered in combination with GDC-6036, on the basis of the following endpoints:
• Plasma concentrations of GDC-6036 and erlotinib at specified timepoints
• Serum concentrations of atezolizumab, cetuximab, and bevacizumab at specified timepoints

The exploratory PK objectives for this study are as follows:
• To evaluate potential relationships between drug exposure and the safety and activity of GDC-6036
• To evaluate the exposure of potential circulating metabolites of GDC-6036 following a single or repeat oral dose(s) of GDC-6036
• To assess ex vivo plasma protein binding of GDC-6036 and its impact on pharmacokinetics (Arm A only)
• To evaluate the effect of GDC-6036 on plasma levels of 4b-hydroxy cholesterol, an endogenous biomarker of CYP3A4 induction (Arm A only)

Immunogenicity Objectives
The immunogenicity objective for this study is to evaluate the immune response to study biotherapeutics on the basis of the following endpoints:
• Incidence of anti-drug antibodies (ADAs) to each study biotherapeutic (atezolizumab, cetuximab, and bevacizumab) during the study relative to the prevalence of ADAs at baseline

The exploratory immunogenicity objective for this study is to evaluate potential effects of detectable ADAs on the basis of the following endpoints:
• Correlation between ADA status for each study biotherapeutic and efficacy, safety, and PK endpoints

Activity Objectives
The activity objective for this study is to make a preliminary assessment of the activity of GDC 6036 as a single agent and in combination with other anti-cancer therapies on the basis of the following endpoints:
• Objective response rate (ORR), defined as the proportion of patients with a complete response (CR) or partial response (PR) on two consecutive occasions >= 4 weeks apart, as determined by the investigator according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)
• Duration of response (DOR), defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause during the study (whichever occurs first), as determined by the investigator according to RECIST v1.1
• Progression-free survival (PFS), defined as the time from first treatment at Cycle 1 Day 1 to the first occurrence of disease progression or death from any cause during the study (whichever occurs first), as determined by the investigator according to RECIST v1.1

Biomarker Objective
The exploratory biomarker objective for this study is to identify and/or evaluate biomarkers that are potentially predictive of response to GDC-6036 as a single agent or in combination with other anti-cancer therapies (i.e., predictive biomarkers), early surrogates of activity, associated with progression to a more severe disease state (i.e., prognostic biomarkers), associated with acquired resistance to KRAS G12C inhibitors (e.g., GDC 6036), associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), can provide evidence of GDC-6036 activity as a single agent or in combination with other anti-cancer therapies (i.e., pharmacodynamic [PD] biomarkers), or can increase the knowledge and understanding of disease biology and drug safety. Corresponding biomarker endpoints include the following:
• Relationship between exploratory biomarkers in blood, plasma, and tumor tissue and safety, PK, activity, or other biomarker endpoints

Study design

This is a first-in-human Phase Ia/Ib, open-label, multicenter dose-escalation and dose-expansion study designed to evaluate the safety, pharmacokinetics, and preliminary activity of GDC-6036 as a single agent and in combination with other anti-cancer therapies in patients with advanced or metastatic solid tumors that harbor the KRAS G12C mutation. The combination therapies in this study are atezolizumab (Arm B), cetuximab (Arm C), bevacizumab (Arm D), and erlotinib (Arm E) in NSCLC, CRC, and solid tumors. The study is designed with the intention to include new, additional treatment arms during study conduct (via protocol amendments) to explore combinations of GDC-6036 with other anti-cancer therapies based on emerging nonclinical and clinical data with GDC-6036, other KRAS G12C inhibitors, or evolving standard-of-care treatment. Anticipated future combinations with GDC-6036 may include RTK/RAS/MAPK

pathway-targeting therapies, agents that target compensatory pathways that may mediate intrinsic or acquired resistance to treatment, immunotherapies, agents that modulate the tumor microenvironment, and standard-of-care agents to further explore safety, pharmacokinetics, and preliminary activity.

Patients who do not meet the criteria for participation in this study (screen failure) may qualify for up to two re-screening opportunities (for a total of three screenings per participant) at the investigator's discretion. Patients are not required to re-sign the consent form if they are re-screened within 30 days after previously signing the consent form. For patients who are re-screened, all eligibility criteria must be re-evaluated and screening assessments should be repeated as applicable to meet the eligibility criteria. The investigator will record reasons for screen failure in the screening log.

Patients will be enrolled in two stages: a dose-escalation stage (Stage I) and a dose-expansion stage (Stage II). Patients will be assigned to one of five regimens: A) Single-agent GDC-6036 (patients with NSCLC, CRC and solid tumors), B) GDC-6036 + atezolizumab (NSCLC only), C) DC-6036 + cetuximab (CRC only), D) GDC-6036 + bevacizumab (solid tumors only) of E) GDC-6036 + bevacizumab (NSCLC only).

During the dose-escalation stage, patients will be evaluated for DLTs at escalating dose levels to determine the maximum tolerated dose (MTD) or maximum administered dose (MAD, if the MTD was not identified) for GDC-6036 as a single agent and in combination with other anti cancer therapies.

In Stage I Arm A (single agent GDC-6036), the starting dose of GDC-6036 will be 50 mg by mouth (PO) once a day (QD).
In the combination arms in Stage I, the starting dose of GDC-6036 will be no higher than one dose level below the last cleared dose level in Stage I Arm A (GDC-6036 single-agent dose escalation).

The starting dose and schedule of the combination therapy agents will be as follows: atezolizumab 1200 mg IV on Day 1 of 21-day cycles; cetuximab as an initial dose of 400 mg/m2 IV followed by 250 mg/m2 IV weekly in 21-day cycles; bevacizumab 15 mg/kg IV on Day 1 of 21-day cycles; and erlotinib 150 mg PO QD in 21 day cycles.

To acquire additional PK and safety data, and tumor PD data related to the mechanism of action of GDC-6036, patients with advanced or metastatic KRAS G12C-positive solid tumors may be enrolled in backfill cohorts in Stage I Arm A (single agent GDC-6036) at dose levels that do not exceed the last cleared dose in Arm A based on the dose-escalation rules described in the protocol. Patients may be enrolled in the Stage I Arm A Backfill Biopsy or Stage I Arm A Backfill Non-Biopsy NSCLC cohort, as described in the protocol. Patients enrolled to backfill cohorts will not be included as part of the DLT-evaluable population.

Approximately 140 additional patients may be enrolled in the dose-expansion stage (Stage II) at or below the MTD (or MAD, if the MTD was not identified) established during Stage I in each arm to further assess the safety, tolerability, PK, and preliminary anti-tumor activity of GDC-6036 as a single agent and in combination with other anti cancer therapies. Furthermore, a subset of up to approximately 15 patients enrolled in Stage II Arm A1, Arm A2, or Arm A3 will participate in the tablet PK assessment.

The study consists of a screening period of up to 28 days, a treatment period, and a safety follow-up period during which patients will be followed for safety outcomes for a treatment-specific period after their final dose of study drug or until they receive another anti-cancer therapy, whichever occurs first. Patients who provide a separate consent may be screened for KRAS G12C mutation status through central testing of circulating tumor DNA (ctDNA).

In the absence of unacceptable toxicities and unequivocal disease progression as determined by the investigator, patients may continue treatment with GDC-6036 until the end of the study.

All patients will be closely monitored for adverse events throughout the study and for a treatment-specific period after the final dose of study treatment or until initiation of another anti-cancer therapy, whichever occurs first.
Adverse events will be graded according to the NCI CTCAE v5.0.
To characterize the PK properties of GDC-6036, plasma samples will be taken at various timepoints before and after dosing.
Approximately 236 patients are expected be enrolled in this study, at approximately 70 investigative sites in North America, Europe, and Asia-Pacific.

Dose-Escalation Stage (Stage I Arm A)

Approximately 96 patients will be enrolled in the dose-escalation stage of the study.

Dose Escalation of Single Agent GDC-6036 (Arm A)
Approximately 48 patients will be enrolled in the dose-escalation stage (Stage I Arm A), including backfill cohorts. The starting dose of GDC-6036 in the dose-escalation stage will be 50 mg PO QD. Single-patient dose-escalation cohorts will be treated at escalating dose levels of GDC-6036. Upon occurrence of a DLT, as defined in the protocol, or a Grade >= 2 adverse event involving major organ toxicity that, per investigator, has no clear identifiable cause other than study drug, dose escalation will convert to a 3+3 design, and the cohort will be expanded to a minimum of 3 patients and follow the dose-escalation rules for 3+3 dose-escalation cohorts (see the protocol). In addition, dose escalation will convert to a 3+3 design at any dose level that exceeds 200 mg QD. Dose escalation may also convert to a 3+3 design based on cumulative PK data relative to exposure targets from nonclinical studies (e.g., in vitro apparent KRAS G12C alkylation concentration associated with 90% target

inhibition [IC90]).

Once single-patient dose escalation converts to a 3+3 dose-escalation design, the cohort undergoing assessment, and all subsequent cohorts, will continue in accordance with the 3+3 dose-escalation cohort rules described in the protocol. Enrollment of the first 2 patients in all 3+3 dose-escalation cohorts will be separated by at least 24 hours.

Patients will be closely monitored for adverse events during a DLT assessment window, defined as Days 1*-1 of Cycle 1. Adverse events identified as DLTs, as defined in the protocol, will be reported to the Sponsor within 24 hours.

Patients who discontinue from study treatment prior to completing the DLT assessment window for reasons other than a DLT will be considered non-evaluable for dose-escalation decisions and MTD or MAD assessments, and will be replaced by an additional patient at that same dose level. Patients who miss more than 5 doses of GDC-6036 during the DLT assessment window for reasons other than a DLT will also be replaced. Patients who reduce the GDC-6036 dose during the DLT assessment window for reasons other than DLT may be replaced. Patients who receive supportive care during the DLT assessment

Intervention

The investigational medicinal products for this study are GDC-6036, atezolizumab, cetuximab, bevacizumab, and erlotinib.

GDC-6036
GDC-6036 will be supplied by the Sponsor as an active pharmaceutical ingredient (API) powder-in-capsule (PIC) formulation in three strengths: 5 mg, 25 mg, and 100 mg (free base equivalent). Additionally, a film-coated tablet formulation in a dose strength of 100 mg (free base equivalent) will also be supplied for clinical use.

In Stage I Arm A, the starting dose of GDC-6036 is 50 mg PO QD. Dose escalations will occur as described in the protocol.

On Day 1 of Cycle 1 of each DLT-evaluable cohort and Stage I Arm A backfill cohort (non-biopsy NSCLC patients only), a single dose of GDC-6036 will be administered to patients in a clinical setting that can accommodate frequent blood draws over a period of up to 8 hours after the first dose is administered and at 24 and 48 hours postdose. QD dosing will begin on Day 3 of Cycle 1. From Cycle 2 onwards, patients will be administered GDC-6036 PO QD on all days of the cycle. The length of Cycle 1 and all subsequent cycles will be 21 days.

In Stage I Arm A backfill cohorts (biopsy patients only) and Stage II expansion cohorts, QD dosing of GDC-6036 will begin on Day 1 of Cycle 1 and each cycle will be 21 days in length.

For GDC-6036 doses to be administered at home, a sufficient number of capsules or tablets should be dispensed to the patient to last until the next visit, or at the investigator*s discretion, through one cycle. Patients will self-administer GDC-6036 as detailed below, except on study visit days when GDC-6036 will be administered in the clinic.

Patients should take GDC-6036 at approximately the same time each day unless otherwise instructed. Patients will be instructed as to the number and strength of capsules or tablets to take, according to their assigned dose level and schedule. Patients will be asked to record the time and date that they take each dose in a medication diary.

Atezolizumab
Atezolizumab will be supplied by the Sponsor as an IV formulation in 1200 mg/20 mL vials, or supplied by the study sites and reimbursed by the Sponsor. Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle, following administration of GDC-6036.

Cetuximab
Cetuximab will be supplied by the Sponsor in commercially available formulations, or supplied by the study sites and reimbursed by the Sponsor. Cetuximab will be administered at an initial dose of 400 mg/m2 as a 120-minute IV infusion on Day 1 followed by 250 mg/m2 as a 60-minute IV infusion weekly, in 21-day cycles. The maximum infusion rate must not exceed 10 mg/min. Cetuximab should be administered following administration of GDC-6036.

Bevacizumab
Bevacizumab will be supplied by the Sponsor as an IV formulation in 400 mg/16 mL vials, or supplied by the study sites and reimbursed by the Sponsor. Bevacizumab will be administered by IV infusion at a fixed dose of 15 mg/kg IV on Day 1 of each 21-day cycle, following administration of GDC-6036.

Erlotinib
Erlotinib will be supplied by the Sponsor as tablets in 25 mg, 100 mg, and 150 mg strengths, or supplied by the study sites and reimbursed by the Sponsor. Erlotinib will be administered PO QD starting at 150 mg in 21-day cycles, at the same time as GDC-6036, with sips of water in between.

GDC-1971
For GDC-1971 doses to be administered at home, a sufficient number of capsules or tablets should be dispensed to the patient to last until the next visit, or at the investigator*s discretion, through one cycle. Patients will self-administer GDC-1971 as detailed below, except on study visit days when GDC-1971 will be administered in the clinic.

Patients should take GDC-1971 at approximately the same time each day unless otherwise instructed. Patients will be instructed as to the number and

strength of capsules or tablets to take, according to their assigned dose level and schedule.

Study burden and risks

KRAS is the most frequently mutated oncogene in up to 25% of cancers and is associated with resistance to select standard-of-care therapies and overall poor prognosis. Although previously considered an *undruggable* cancer target, the landmark discovery of the switch II pocket within KRAS has enabled the development of covalent inhibitors specific for KRAS G12C. With this finding, covalent small molecule inhibitors targeting KRAS, and specifically the KRAS G12C mutation, are being evaluated in early clinical development.

The study assessments will be at the screening, C1D1 (cycle 1, day 1), (C1D2 - arm A only), C1D3, C1D8, C1D15, C2D1, C2D15, C3D1, C3D15, C4D1, C4D15, C5D1, C5D15, C6D1, C6D15, CxD1 of each subsequent cycle. Treatment will continue until disease progresses (as defined by RECIST criteria), unacceptable toxicity occurs, patient is out of clinicial benefit, patient withdraws or dies, or patient discontinues the study for any other reason, after which all patients make a final visit.

The potential side effects, based on laboratory studies or knowledge of similar drugs, for GDC-6036 are: Diarrhea, Nausea, Vomiting, Mouth or throat irritation, Abnormal liver tests (possible liver damage), Sensitivity to sunlight and Genotoxicity (damage to the genetic information within a cell).
During the study assessments the patient could experience the following discomforts:
Response to contrast medium (used for CT scan / MRI)
Possible consequences of blood sampling (pain, bruising, infection, dizziness)
Radiation exposure on CT scan
Possible consequences of biopsy (pain, redness, swelling, bleeding)

Specific therapies aimed at KRAS G12C-positive cancer may provide more tolerable and effective treatment options for patients with advanced stage cancers that harbor KRAS G12C. Based on the nonclinical data available for GDC-6036 and on clinical data from other covalent KRAS G12C inhibitors, the benefit-risk profile of GDC-6036 as a single agent has been assessed to be appropriate for initiating this first-in-human clinical study.

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

• Histologically documented advanced or metastatic solid tumor with KRAS G12C mutation • Age > 18 years at time of signing Informed Consent Form • Women of childbearing potential must agree to remain abstinent or use contraception, and agree to refrain from donating eggs during the treatment period and after the final dose of study as specified in the protocol • Men who are not surgically sterile must agree to remain abstinent or use contraception, and agreement to refrain from donating sperm during the treatment period and after the final dose of study treatment as specified in the protocol

Exclusion criteria

• Malabsorption or other condition that interferes with enteral absorption
• Active brain metastases
• Clinically significant cardiovascular dysfunction or liver disease

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	21-09-2021
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Avastin
Generic name:	Bevacizumab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Erbitux
Generic name:	Cetuximab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	RO7435846-GDC-6036
Generic name:	GDC-6036
Product type:	Medicine
Brand name:	Tarceva
Generic name:	Erlotinib
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Tecentriq

Generic name:	Atezolizumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	22-02-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-05-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-06-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-07-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-10-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-12-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-02-2022

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-06-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-12-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-03-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-06-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-08-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-11-2023
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
EU-CTR	CTIS2023-506311-18-00
EudraCT	EUCTR2020-000084-22-NL
Other	IND 147339; NCT04449874
CCMO	NL75606.056.20