A Phase Ib/II, open-label, multicenter study of INC280 in combination with buparlisib in adult patients with recurrent glioblastoma

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Phase Ib: To estimate the MTD and/or RP2D of INC280 in combination with buparlisib in patients with recurrent glioblastoma.Phase II: To estimate the anti-tumor activity of INC280 single agent and in combination with buparlisib in patients with...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Miscellaneous and site unspecified neoplasms benign
Study type	Interventional

Summary

ID

NL-OMON45098

Source
ToetsingOnline

Brief title
Phase Ib/II trial: INC280 and BKM120 in recurrent glioblastoma

Condition

- Miscellaneous and site unspecified neoplasms benign

Synonym
Malignant high-grade astrocytoma, primary brain tumor grade 4

Research involving
Human

Sponsors and support

Primary sponsor: Novartis

Source(s) of monetary or material Support: Novartis Pharma B.V.

Intervention

Keyword: buparlisib, c-MET mutation, INC280, PTEN

Outcome measures

Primary outcome

-Phase Ib: Incidence of dose limiting toxicities (DLTs)

-Phase II: Progression free survival rate (PFSR)

-Surgical arm: Concentrations of INC280 and buparlisib in tumor

Secondary outcome

-Type, frequency, and severity of adverse events and serious adverse events.

-Tolerability: dose interruptions, reductions and dose intensity.

-Plasma concentration of INC280 and buparlisib, and PK parameters, including

but not limited to Cmax, Tmax, AUCtau, and T1/2.

-Overall response rate (ORR)

-Overall survival (OS)

Study description

Background summary

Glioblastoma accounts for over 50% of all gliomas with an annual incidence rate of 3 to 4 cases per 100,000 persons, resulting in 240,000 new cases worldwide each year. The current standard treatment consists of neurosurgery followed by radiotherapy and adjuvant temozolomide.
Almost all patients will experience recurrent disease, and the median progression-free survival (PFS) is approximately 6 months.
Bevacizumab is approved for the treatment of recurrent glioblastoma. However, most patients experience relapse. Options for salvage remain extremely limited. Hence novel agents targeting relevant pathways are desperately needed.

Genetically, glioblastoma is characterized by complex chromosome abnormalities that control the process of cellular proliferation, survival, invasion and angiogenesis. Recent insights into the biology of gliomas suggested that deregulation of PI3K signaling pathways and activation of tyrosine kinase receptors including cMET, play essential roles in tumor initiation and maintenance.

In glioblastoma, loss of PTEN function by mutation or gene deletion is the most the common form of PI3K pathway deregulation. A wide spectrum of PI3K pathway inhibitors are currently in clinical development, including buparlisib. Preclinical evidence suggested PTEN deficient cancers depend more on PIK3CB. Therefore, buparlisib, which has demonstrated clear evidence of target inhibition, preliminary antitumor activity, and good brain penetrance capability, is a good treatment option for inhibiting PTEN in glioblastoma.

Inhibition of MET signaling can have potent anti-tumor effects, including regression of human glioblastoma tumor xenografts. MET inhibitors (like INC280) are currently being evaluated in clinical trials in several cancers. In view of the complex, heterogeneous nature of glioblastoma, and the clinical activity observed in current ongoing trials, outcome remains grave. Hence, new or novel approaches aimed at improving the outcome for patients with recurrent glioblastoma are needed.

The development of combination therapy strategically targeting multiple steps at the PI3K and MET signaling pathways may improve the approach in this group of patients who failed first or second-line treatment after recurrent glioblastoma.

Study objective

Phase Ib: To estimate the MTD and/or RP2D of INC280 in combination with buparlisib in patients with recurrent glioblastoma.
Phase II: To estimate the anti-tumor activity of INC280 single agent and in combination with buparlisib in patients with recurrent glioblastoma.
Surgical arm: To estimate the concentrations of INC280 and buparlisib in tumor tissue (tumor sample).

Study design

A multi-center, open-label, phase Ib/II study.

Intervention

Treatment with INC280 single agend and in combination with BKM120 (buparlisib).

Study burden and risks

-Possible toxicity derived from the study treatment. The known adverse events are documented in the informed consent form.
-The study assessments are used in routine practice: venepuncture (fasting), echocardiogram or MUGA scan, CT scan or MRI, ECG, lumbar puncture. A flowchart with all these assessments can be found in the informed consent form.
-Completion of questionnaires (8 times)
-Collection of urine during 24 hours (possibly once)
-Adequate contraception
-Frequent study visits

Contacts

Public
Novartis

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Scientific
Novartis

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

** 18 years of age.

*Histologically confirmed diagnosis of glioblastoma after initial tumor resection with radiographic evidence of recurrent tumor per RANO criteria.
*Phase I: Documented evidence of PTEN mutations, homozygous deletion of PTEN or PTEN negative (H Score < 10) by IHC confirmed by local documentation (phase Ib only) or central assessment
*Phase II: Documented evidence of PTEN mutations, homozynous deletion of PTEN or PTEN negative (H score < 10) by IHC or c-Met amplification (GCN > 5) by FISH, all assessed centrally. Fusion transcripts or mutant c-Met (based on local data) may be eligible for single agent arm after documented agreement with Novartis.
*Must have received the following treatment for glioblastoma:
*Prior adjuvant treatment with radiotherapy and temozolomide;
*A maximum of two prior chemotherapy/antibody regimens (including bevacizumab or other direct VEFG/VEGFR inhibitors) for recurrent disease are permitted.
*Representative archival glioblastoma sample (formalin-fixed paraffine embedded tissue) must be available.
*ECOG performance status * 2.
*Able to swallow and retain oral medication.
*Patients in the surgical arm only: patients with recurrent glioblastoma must be eligible for surgical resection as deemed by the site Investigator.

Exclusion criteria

*Prior or current treatment with a c-MET inhibitor or HGF-targeting therapy
*Prior treatment with a PI3K and/or mTOR inhibitors for glioblastoma (applicable for combination treatment arm only).
*Receiving treatment with medications that are known strong inhibitors or inducers of CYP3A, and cannot be discontinued 7 days prior to the start of the treatment and during the course of the study.
* Receiving treatment with medications that are known CYP3A or CYP1A2 substrates with narrow therapeutic index, and cannot be discontinued during the course of the study.
* Receiving treatment with long acting proton pump inhibitors, and cannot be discontinued 3 days prior to the start of INC280 treatment and during the course of the study.
*Currently being treated with Enzyme Inducing Anti-Epileptic Drug (EIAED). If previously on an EIAED, the patient must be off of it for at least 2 weeks prior to study treatment.
*Currently receiving warfarin or other coumadin-derived anticoagulants for treatment, prophylaxis or otherwise.
*Currently receiving increasing or chronic treatment (> 5 days) with corticosteroids or another immunosuppressive agent.
*History of acute or chronic pancreatitis or any risk factors that may increase the risk of pancreatitis.
*Active cardiac disease or a history of cardiac dysfunction.
*Impairment of gastrointestinal (GI) function or GI disease that might significantly alter the absorption of study drug
*Medically documented history of or active major depressive episode, bipolar disorder (I or II), obsessive-compulsive disorder, schizophrenia, a history of suicidal attempt or ideation, or

homicidal ideation (e.g. risk of doing harm to self or others), or patients with active severe personality disorders (defined according to DSM- IV).
*Anxiety * CTCAE grade 3
*Any of the following baseline laboratory values:
*Hemoglobin < 9 g/dL
*Platelet count < 75 x 109/L
*Absolute neutrophil count (ANC) < 1.0 x 109/L
*INR > 1.5
*Serum lipase > normal limits for the institution
*Asymptomatic serum amylase > grade 2
*Potassium, magnesium, and calcium (corrected for albumin) > normal limits for the institution
*Total bilirubin >1.5 x ULN
*Serum creatinine >1.5 x ULN or creatinine clearance * 45 mL/min
*Alanine aminotransferase (AST) or aspartate aminotransferase (ALT) > 3.0 ULN (or > 5.0 x ULN if liver metastases are present)
*Fasting plasma glucose > 120mg/dL or > 6.7 mmol/L
*HbA1c > 8%.
* Pregnant or nursing (lactating) women

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):	14-04-2014
Enrollment:	10
Type:	Actual

Ethics review

Approved WMO

Date:	16-09-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	26-02-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	27-02-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	15-09-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	19-09-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	23-10-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	19-12-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	30-12-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	13-02-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO	

Date:	04-03-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	22-04-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	24-04-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	26-05-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	28-05-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	15-07-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	25-08-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	21-09-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	14-10-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO	

Date:	07-01-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	08-01-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	19-05-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	12-07-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	13-07-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	26-07-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	01-12-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	EUCTR2013-000699-14-NL
ClinicalTrials.gov	NCT01870726
CCMO	NL45781.041.13