BRF113928: A Phase II study of the BRAF inhibitor dabrafenib as a single agent and in combination with the MEK inhibitor trametinib in subjects with BRAF V600E mutation positive metastatic (stage IV) non-small cell lung cancer

Published: 10-01-2013
Last updated: 25-04-2024

Primary: overall response rate.Secondary: progression free survival, duration of response, overall survival, safety, tolerability, pharmacokinetics (PK).

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Respiratory tract neoplasms
Study type	Interventional

Summary

ID

NL-OMON47910

Source
ToetsingOnline

Brief title
BRF113928

Condition

- Respiratory tract neoplasms

Synonym
non-small cell lung cancer; lung cancer

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma BV

Intervention

Keyword: BRAF, Dabrafenib, NSCLC, Trametinib

Outcome measures

Primary outcome

Overall response rate.

Secondary outcome

Progression free survival, duration of response, overall survival, safety,

tolerability, PK.

Study description

Background summary

For patients diagnosed with advanced non-small cell lung cancer (NSCLC), conventional cytotoxic chemotherapy remains the standard treatment and offers only a modest survival benefit. Therefore, more innovative approaches are needed to improve the therapy of this deadly disease. One approach is to identify specific genomic changes in different lung cancer patients and treat them with agents directed against those genetic changes. One specific genomic change present in approximately 2% of lung cancers is a BRAF mutation. BRAF is a serine/threonine kinase that lies downstream of RAS in the RAS/RAF/MEK/ERK signaling pathway, a key molecular cascade that regulates cell growth, proliferation and differentiation. Mutations in the BRAF gene, the vast majority of which are V600E missense mutations, are most commonly seen in melanoma, but are also detected in approximately 2% of NSCLC. Importantly, most cancer cells harboring a V600E BRAF mutation display a critical dependence on the activity of this oncogene for their growth and survival, and are extremely sensitive to selective BRAF and MEK inhibitors, irrespective of tissue of origin. This study will investigate the effects of GSK2118436 administered as a single agent to subjects with stage IV NSCLC whose tumors carry a V600E BRAF mutation.

In protocol amendment 8 an extra arm is introduced: dabrafenib plus trametinib, while subjects with disease progression when on dabrafenib monotherapy are given the option to continue treatment with dabrafenib in combination with trametinib.

In protocol amendment 9 another extra arm is introduced: 25-40 first line patients. They will betreated with the combination therapy.

Study objective

Primary: overall response rate.
Secondary: progression free survival, duration of response, overall survival, safety, tolerability, pharmacokinetics (PK).

Study design

Phase II, non-comparative, open-label, study. Treatment with dabrafenib 150 mg twice daily lus or minus trametinib 2 mg twice daily until disease progression or unacceptable adverse events. Th last 40 subjects to be included will be treated with the combination therapy.
Subjects enrolled in the primary study cohort will be required to have relapsed or progressed on one or more platinum based chemotherapy prior to enrolment (i.e., dabrafenib will be no less than second line treatment for metastatic disease). The expansion cohort will allow subjects that have received prior treatment as well as treatment naive subjects where dabrafenib will be first line treatment in the metastatic setting.
Interim-analysis after 20 subjects have either withdrawn from the study before response is assessed or have at least 2 post-baseline scans.
The study will be considered completed when a minimum of 70% of subjects have died or 5 years have passed since the last subject was entered on the study, whichever comes first. Subjects who are still benefiting from dabrafenib at the time of study completion may have the option to enter a follow-up study.
Approx. 140 patients.

Cohort A: Monotherapy (dabrafenib 150 mg BID) approximately 60 at least 2nd line subjects with BRAF V600E NSCLC centrally confirmed.
Cohort B: Combination therapy (dabrafenib 150 mg BID and trametinib 2 mg once daily); approximately 40 at least 2nd line subjects with BRAF V600E NSCLC subjects centrally confirmed.
Cohort C: Combination therapy (dabrafenib 150 mg BID and trametinib 2 mg once daily); approximately 25-40 1st line subjects with BRAF V600E NSCLC centrally confirmed:

Intervention

Treatment with dabrafenib plus or minus trametinib.

Study burden and risks

Risk: adverse events of study treatment.
Burden: Visits screening, start, week 3, 6, 9 and thereafter every 3 weeks.
After disease progression: follow-up for survival (by phone if needed).
Tests etc. until progression:
Physical examination every visit (2 times incl. rectal/vaginal examination), regular skin inspection. Eye examination twice and more frequently in case of signs or symptoms.
Blood tests every visit ,10-15 mL.
CT/MRI scan chest and abdomen (if indicated: more extensive) every 6 weeks until week 36, thereafter every 12 weeks (as during regular treatment).
Pregnancy tests at screening.
Tumor biopsy (from prior procedure, if needed fresh sample) for assessment BRAF mutation at screening.
ECG 3x in first 6 weeks, thereafter every 9 weeks.
Echocardiogram 2x in First 6 weeks, thereafter every 9 weeks.
Optional sub-studies:
- pharmacogenetic (1x, 6 mL blood).
- Tumor biopsy at screening, after 6 week and at progression.
- Skin biopsy in case of skin lesions.
- Tumor biopsy in case of new tumor.
Most tests are not different from regular treatment in nature and frequency.
Extra are the echocardiography, theskin examinations and the optional tests.

Contacts

Public
Novartis

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Scientific
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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 or cytologically confirmed NDCLC stage IV.
* Documented disease progression (primary study cohort). Subjects in Cohort C will be
required to have not received prior systemic anti-cancer therapies for metastatic disease
* Measurable disease.
* 18 years and above.
* Life expectancy at least 3 months.
* ECOG performance status 0-2.
* Presence of a V600E BRAF mutation in lung cancer tissue.
* Females of childbearing potential: adequate method of contraception.

Exclusion criteria

* Previous treatment with a BRAF or MEK inhibitor.
* Anti-Cancer therapy including chemotherapy, radiation-therapy, immunotherapy, biologic therapy or major surgery within 14 days prior to start of study therapy.
* Active GI disease or other condition that will interfere significantly with the absorption of drugs.
* Brain metastases (exceptions see protocol page 30)
* A history or evidence of cardiovascular risk (see protocol page 30 for details).
* Pregnancy or breastfeeding

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	16-05-2013
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Mekinist
Generic name:	Trametinib
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Tafinlar
Generic name:	Dabrafenib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	10-01-2013
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-02-2013
Application type:	First submission

Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	27-02-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-05-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-05-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-11-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	15-01-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	27-06-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	15-07-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO

Date:	28-08-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-09-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	30-01-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	02-02-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-01-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	26-01-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	26-04-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-05-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United

	(Nieuwegein)
Approved WMO Date:	05-10-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	06-10-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	14-03-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-03-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	07-09-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-09-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	26-04-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	30-05-2018

Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-07-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-07-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	06-11-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-01-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	30-01-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-11-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	06-12-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	05-02-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	17-02-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	08-10-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	14-10-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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
Other	BRF113928, www.gsk-clinicalstudyregister.com
EudraCT	EUCTR2011-001161-41-NL

Register	ID
CCMO	NL43103.060.12