A phase Ib dose escalation/randomized phase II, multicenter, open-label study of BYL719 in combination with cetuximab in patients with recurrent or metastatic head and neck squamous cell carcinoma

Published: 10-12-2012
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Primary objective: Phase Ib: To estimate the MTD and/or RP2D of BYL719 in combination with cetuximab. Phase II: To compare the efficacy of BYL719 plus cetuximab in comparison with cetuximab monotherapy.Secondary objective (major): safety and...

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

Summary

ID

NL-OMON40123

Source
ToetsingOnline

Brief title
BYL719 and cetuximab in head and neck carcinoma

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
Head and neck cancer

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Farmaceutische industrie.

Intervention

Keyword: BYL719, cetuximab, Head and neck carcinoma

Outcome measures

Primary outcome

Incidence of DLTs (phase Ib), progression free survival (phase II).

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Phase Ib Arm-C: AUCO-24

Secondary outcome

Adverse events, dose interruptions, reductions, dose density, PK (phase IB),

overall response rate, disease control rate, overall survival, overall survival

rate at month 6.

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Plasma concentration vs. time profiles, plasma PK parameters of BYL719 in Arm C

Study description

Background summary

EGFR (epidermal growth factor receptor) is overexpressed in around 90% of the HNSCC (head and neck squamous cell carcinoma) and is therefore a therapeutic target for cancer treatment. However, many patients are refractory to anti-EGFR treatment, due to mechanisms of resistance. An established finding in the tumors refractory to EGFR inhibition is the activation of the PI3K/AKT/mTOR

pathway leading to enhanced cell survival. Combination therapy with cetuximab and a PI3K inhibitor could potentially help overcome this resistance. In preclinical models, the combination of the alpha-specific PI3K inhibitor BYL719 with cetuximab demonstrated significant antitumor efficacy and strong synergy in HNSCC cell lines in vitro and in tumor xenografts in vivo.
In clinical trials, preliminary data on tolerability and first signs of efficacy in colorectal cancer and HNSCC patients treated with cetuximab in combination with a PI3K inhibitor PX-866 have been reported. This study suggests that inhibition of the PI3K pathway combined with a block of EGFR may be used safely in patients and could lead to increased clinical efficacy.
In summary, these results provide a strong rationale for the combination therapy of cetuximab and BYL719 in cancers where the EGFR/PI3K/AKT pathway is activated. Both the Phase Ib and Phase II parts of the study will be conducted in adult patients with RM HNSCC who are resistant or ineligible or intolerant to platinum-containing chemotherapy.
The primary purpose of the dose escalation part is to estimate the MTD and/or to determine the recommended phase II dose (RP2D) of the orally administered PI3K inhibitor BYL719 in combination with cetuximab. Once MTD/RP2D has been determined, additional patients will be enrolled in Phase II to assess the anti-tumor activity of BYL719 in combination with cetuximab vs. cetuximab single-agent, and to further characterize the safety and tolerability of the drug combination.

Study objective

Primary objective: Phase Ib: To estimate the MTD and/or RP2D of BYL719 in combination with cetuximab. Phase II: To compare the efficacy of BYL719 plus cetuximab in comparison with cetuximab monotherapy.
Secondary objective (major): safety and tolerability, PK.

PROTOCOL AMENDMENT 5 added primary objective for phase ib part
*Arm C: To compare the pharmacokinetics of the dispersible tablet formulation of BYL719 in combination with cetuximab in patients with RM HNSCC with Arm A

Study design

Open-label phase Ib dose escalation and randomized phase II study.
Approximately 111 patients (20 for phase Ib and 99 for phase II).
The aim of phase Ib (n~12) is to determine the MTD and/or RP2D of BYL719 in combination with fixed-dose cetuximab. Cycles of 4 weeks. Cohorts of 3-6 patients. Bayesian logistic regression model.

ARM A: Patients with no swallowing dysfunction (BYL719 whole tablets + cetuximab)
ARM B: Patients with swallowing dysfunction (crushed BYL719 tablets + cetuxmab)

PROTOCOL AMENDMENT 5:
added
ARM C: Patients with swallowing dysfunction with PEG-sonde or G-sonde (BYL719 dispers + cetuximab)

Phase II (n~99) will be performed with the highest well-tolerated dose of BYL719 in combination with fixed dose (=SPC recommended dose).

ARM 1 and ARM 2: Randomization (2:1) to this combination or cetuximab in SPC recommended dose as monotherapy. Cetuximab only as induction therapy allowed.

ARM1: Combination BYL719 + cetuximab (N=66)
ARM 2: Cetuximab monotherapy (N=33) -> cross-over to ARM 2B: Combination BYL719 + cetuximab

ARM 3: prior cetuximab therapy in combination with platinum
ARM 3: Combinatie BYL719 + cetuximab (N=40)

Treatment until progression or unacceptable toxicity.
Follow-up for survival (phase II patients).

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Added to PHASE IB part:
*Arm C: To compare the pharmacokinetics of the dispersible tablet formulation of BYL719 in combination with cetuximab in patients with RM HNSCC with Arm A
- Arm C will use a suspension administered via gastric feeding tube (gastrostomy tube, G-tube), in patients with swallowing dysfunction

Intervention

Treatment with cetuximab in combination with BYL719 or cetuximab alone.

Phase Ib part: cetuximab (i.v. 400mg/m2 starting dose followed by weekly 250mg/m2) + BYL719 escalting dose (startdose = 300mg BYL719, oral daily administration).

Phase II part: randomisation 2:1
Arm 1: ~66 patients BYL719 + cetuximab
Arm 2: ~33 patients cetuximab

Arm 3: ~40 patients BYL719 + cetuximab

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BYL719 is availableas film-coated tablets and dipsers (solutable in water)

Study burden and risks

Risk: Adverse events of study medication (BYL719 and cetuximab). The combinations have not yet been tested in humans before.
Side effect seen in BYL719 sofar are hyperglycemia, nausea, fatigue, liver enzyme abnormalities, vomiting, diarrhea, dyspepsia, erythema, flatulence, hypertension, increased tendency to bruise, skin atrophy and hand-foot syndrome

The most important side effects of cetuximab (alone) are skin rash, hypomagnesaemia, headache, diarrhea, infection, infusion reaction (an allergy-like response, sometimes fatal), cardiopulmonary arrest and/or sudden death, interstitial lung disease (scarring of the lung), kidney failure, aseptic meningitis

Other risks caused by assessments during study: radiation due to scans and X-rays, risks and inconvenience due to infusion of cetuximab and blooddraws as local infections, pain and bleeding, risks and inconveniences due to tumorbiopsies as bleeding and pain.

Burden:
Treatment cycles of 4 weeks with weekly cetuximab infusions.
6 visits during cycle 1 and 4 visits in the subsequent cycles. Visit duration 1-4 h. 2 visits (phase Ib, 9 samples of 2,5 ml each per occasion) en 1 visit (phase II, 4 samples of 2,5 ml each) of 8-10 h (serial PK sampling) for BYL719 patients only.
Weekly blood sampling during cycle 1-2 and bi-weekly thereafter. 25-40 ml of blood/cycle, except for cycle 1 (=50-110 ml).
ECGs: 4 during cycle 1, 2 during cycle 2, 1 per cycle thereafter.
Echocardiogram or MUGA-scan at screening and end of treatment.
Tumor evaluations at screening and every 6-8 weeks thereafter until disease progression.
Tumor biopsy at screening and at disease progression.
Follow-up for survival (phase II patients only, phone call every 4 months).

Contacts

Public
Novartis

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Arnhem 6824 DP
NL
Scientific
Novartis

Raapopseweg 1
Arnhem 6824 DP
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Age * 18 years
- Patients with histologically/cytologically-confirmed HNSCC
- Patients must be resistant to platinum-based chemotherapy, or be ineligible or intolerant to platinum-based therapy
- For Phase Ib only, at least 1 prior therapy for recurrent or metastatic disease
- For Phase II only, a maximum of 1 prior therapy for recurrent or metastatic disease
- Prior cetuximab or another EGFR-targeted antibody therapy is allowed only if administered in the induction setting, or concurrently with radiation in the curative setting, with the last dose of cetuximab administered at least 12 months prior to starting the study treatment
- Availability of tumor specimen (primary or metastatic, archival or fresh)
- At least one measurable or non-measurable lesion is required for patients enrolled in Phase Ib. Measurable disease is required for Phase II patients (as per RECIST 1.1 criteria)
- WHO Performance Status (PS) * 2.
- Adequate organ function and laboratory parameters
- Negative serum pregnancy test ;NEW
-For Arm 3, prior cetuximab incl. platinum as therapeutic setting and disease progression documented within 9 months of the last dose of cetuximab administered in that setting.
- Patients enrolled in Arm 3 must have amenable sites to biopsy;More detailed inclusion criteria see protocol section 5.2

Exclusion criteria

- Prior treatment with PI3K-inhibitors

- Patients with a prior serious infusion reaction to cetuximab
- Patients with primary central nervous system (CNS) tumor or CNS tumor involvement
- Clinically significant cardiac disease or impaired cardiac function
- Patients with diabetes mellitus
- Impaired GI function or GI disease that may signifincant alter the absorption of oral BYL719
- History of another malignancy within 2 years prior to starting study treatment ;More detailed exclusion criteria see protocol section 5.3

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	18-03-2013
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Erbitux
Generic name:	cetuximab
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	10-12-2012
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	08-02-2013
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	05-03-2013
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	16-04-2013
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	16-05-2013
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	29-07-2013
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-09-2013
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	10-01-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-03-2014
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Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	

Date:	25-03-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-06-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-07-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-09-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	07-10-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	17-10-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-10-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-10-2014
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Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-12-2014
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Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	

Date:	05-12-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
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Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	08-06-2015
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Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	17-06-2015
Application type:	Amendment
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Approved WMO Date:	03-08-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	07-08-2015
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Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-08-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-10-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
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Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	

Date:	11-12-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2011-006017-34-NL
ClinicalTrials.gov	NCT01602315
CCMO	NL42698.091.12