A Phase II, Open-label, 1:1 Randomized, Controlled Trial Exploring the Efficacy of EMD 1201081 in Combination with Cetuximab in Second-Line Cetuximab-Naive Subjects with Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (R/M SCCHN)

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The primary objective of this trial is to determine if EMD 1201081 (formerly known as IMO-2055) has anti-tumor activity in subjects by examining its effects on accepted clinical endpoints in combination with cetuximab. • To evaluate progression-free...

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

Summary

ID

NL-OMON36270

Source
ToetsingOnline

Brief title
EMR200068-006 (048/062)

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym

Head & Neck Cancer, Squamous Cell Carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Merck KGaA
Source(s) of monetary or material Support: industry;i.e. Merck KGaA

Intervention

Keyword: Head & Neck Cancer, Metastatic Squamous Cell Carcinoma

Outcome measures

Primary outcome

Progression-free survival (PFS) time

Secondary outcome

• Overall response (by RECIST)

• Disease control status (Complete Response [CR] + Partial Response [PR] +

Stable Disease [SD])

• Duration of response

• Overall survival time

• Response rate of subjects treated with EMD 1201081 + cetuximab after they

have progressed on cetuximab alone.

• Time to tumor progression (TTP) in subjects treated with EMD 1201081 +

cetuximab.

• Safety and tolerability

• Incidence, severity, and relationship to the trial drug of treatment-emergent

AEs.

• Serious AEs (including deaths).

• AEs leading to permanent treatment discontinuation.

• Local tolerability (including injection site reactions).

• Clinically relevant changes in routine hematology/coagulation, serum chemistry and urinalysis laboratory tests (according to local laboratory reference ranges).

• Concomitant medications after the start of trial treatment.

• Vital signs.

• Physical examinations.

• Selected exploratory biomarkers (central laboratory).

• The effects of EMD 1201081 on the development of anti-cetuximab antibodies and cetuximab pharmacokinetics (immunogenicity).

Study description

Background summary

EMD 1201081 (IMO-2055) is a novel phosphorothioate oligodeoxynucleotide that is an agonist of Toll-like Receptor 9 (TLR9). TLR9 is a member of the TLR family of pathogen associated molecular pattern recognition receptors. TLR9 is expressed in human B cells and plasmacytoid dendritic cells (pDCs) of the immune system. TLR9 recognizes unmethylated CG dinucleotides that are present in bacterial DNA and compounds that mimic bacterial DNA. Human DNA contains relatively few CG dinucleotides, most of which are in a methylated form that is not recognized by TLR9. Agonists of TLR9 induce an innate immune response that in turn leads to induction of a Th1-type adaptive immune response. The innate and adaptive immune responses generated through TLR9 stimulation produce a profile of cytokines and chemokines that have the potential for significant host responses to tumors, and generate antigen-specific antibodies, cytotoxic T lymphocytes, and expansion of antigen-specific memory T cells [1, 2]. Moreover, there are additional data suggesting that EMD 1201081 has a direct action on growth factor receptors and growth pathways.

Other TLR9 agonists have been explored in oncology. In particular, CpG 7909 (also called agatolimod, Pfizer) has been examined in clinical trials in a

variety of tumor types. In the most advanced studies, CpG 7909 was studied in two Phase III trials in non-small cell lung cancer (NSCLC) in combination with cytotoxic regimens. Preliminary data on the results of this trial were presented in 2008 [3, 4]. The trials did not meet the efficacy endpoint and there were some questions about the safety (particularly hemotologic safety) of combining CpG 7909 and cytotoxic agents. CpG 7909 is still being investigated, but the focus appears to have shifted to targeted agent combinations in small Phase II trials.

The structure of EMD 1201081 is distinctly different from CpG 7909 and other investigational TLR9 agonists. In particular, EMD 1201081, a synthetic oligonucleotide, is designed to be more resistant to exonuclease activity and should therefore be more biologically stable. However, like the other TLR9 agonists, EMD 1201081 is delivered by subcutaneous injection. The mechanism of action is believed to be as follows:
EMD 1201081 binds to TLR9 in immune cells at the injection site. These cells, principally dendritic cells in the skin, are activated and migrate to draining nodes where they have the opportunity to interact to induce a systemic response. Cellular activation and interactions occurring in the lymph nodes then trigger the systemic immune response.

In pre-clinical studies, EMD 1201081 has demonstrated significant anti-tumor activity in combination with cetuximab both with and without cytotoxic agents. Because EMD 1201081 enhances the anti-tumor activity with monoclonal antibodies such as cetuximab in murine xenograft models, it is an attractive potential partner for cetuximab. If EMD 1201081*s promise of enhancing cetuximab activity is upheld, combinations with other monoclonal antibody and targeted agents may be explored as well. Of particular interest, is the finding that EMD 1201081 combined with cetuximab showed anti-tumor activity in xenografts with the k-ras mutation.

Six EMD 1201081 trials have been completed or are ongoing in approximately 180 healthy subjects or patients with advanced malignancies. No significant safety findings were seen in the first trial in healthy volunteers. In that trial, subjects mainly experienced local site injection reactions which resolved after several days. Subjects could also experience flulike symptoms. These findings were also seen in trials in cancer patients where doses as high as 0.64 mg/kg were given for months at a time. A single arm Phase II trial examined the anti-tumor activity of EMD 1201081 in patients with advanced renal cell carcinoma. In this trial, EMD 1201081 mono-therapy did not exhibit anti-tumor activity as prospectively defined in the Simon 2-stage design. However, some patients had stabilized disease for months and were able to tolerate weekly injections of EMD 1201081 for over a year.

EMD 1201081 has also been investigated in combination with cytotoxic and targeted agents. A dose finding trial, primarily in NSCLC patients, explored the tolerability of EMD 1201081 combined with gemcitabine and carboplatin. This

trial of 22 patients suggests that cytotoxic combinations with EMD 1201081 may be possible but require care. Five patients experienced hematological toxicities which met the pre-specified definitions of dose limiting toxicities. This was somewhat similar to side effects seen in two Phase III trials of CpG 7909. However, the small size of the trial and known toxicities of platinum and gemcitabine make it difficult to definitively assign the toxicities to EMD 1201081 or its combination. This suggests establishing EMD 1201081 clinical activity would be more complicated with cytotoxic agents as opposed to targeted therapies. Two dose-finding studies are ongoing where EMD 1201081 is combined with targeted agents. EMD 1201081 combined with erlotinib and bevacizumab is being studied in patients with NSCLC. EMD 1201081 is also being combined with irinotecan and cetuximab in metastatic colon cancer. To date, these trials indicate that these EMD 1201081 combinations appear to be well tolerated. One patient in the NSCLC trial has been on study for over a year. No significant changes in the safety profile have emerged.

Study objective

The primary objective of this trial is to determine if EMD 1201081 (formerly known as IMO-2055) has anti-tumor activity in subjects by examining its effects on accepted clinical endpoints in combination with cetuximab.
• To evaluate progression-free survival time of subjects treated with EMD 1201081 + cetuximab compared to cetuximab alone in cetuximab-naïve subjects with recurrent and/or metastatic SCCHN who have progressed on a cytotoxic therapy.

Secondary objectives
• To evaluate the overall response (by RECIST 1.0) or disease control status (CR + PR + SD) of subjects treated with EMD 1201081 + cetuximab compared to cetuximab alone in subjects with R/M SCCHN.
• To evaluate the duration of response of subjects treated with EMD 1201081 + cetuximab compared to cetuximab alone in subjects with R/M SCCHN.
• To evaluate overall survival time in subjects treated with EMD 1201081 + cetuximab as second-line treatment.
• To study the safety and tolerability of the combination EMD 1201081 + cetuximab in the overall trial population.
• To assess the response rate of subjects treated with EMD 1201081 + cetuximab after they have progressed on cetuximab alone.
• To evaluate the effects of EMD 1201081 on the development of anti-cetuximab antibodies and cetuximab pharmacokinetics (immunogenicity).
• To evaluate the time to tumor progression in subjects treated with EMD 1201081 + cetuximab.
• To characterize selected biomarkers in consenting subjects.
Exploratory biomarker research objectives
• To assess the influence of genetic variations (subject germline DNA) on subject response to treatment. (Note: This is optional and conditioned on the signature of a specific Informed Consent Form.)

• To assess circulating protein markers (e.g. cytokines and chemokines) and immune cell subsets during the course of therapy and their influence on subject response to treatment.
• To investigate potential markers of EMD 1201081 immune activation and effects on cellular immunity.
• To assess the expression of genes in whole blood (i.e. gene expression from cells circulating in the blood) and their evolution during the course of therapy and their influence on subject response to treatment.
• To assess the influence of mutations in the tumors on subject response to treatment.
• To assess the influence of expression of certain proteins or genes, in the tumor, on subject response to treatment.

Study design

The study will be conducted as a Phase II, open label, 1:1 randomized, controlled trial. Subjects will be randomized to receive cetuximab in combination with EMD 1201081 (Arm A) or cetuximab alone (Arm B = control arm). The total subject treatment period is estimated to be approximately 18 months (accrual period of 12 months, starting with first subject randomized, followed by a follow-up period of 6 months, starting with last subject randomized) after which the main (proof-of-concept) analysis will be performed. Subjects will be treated in their treatment arm until progression of their disease. Subjects in the cetuximab control arm may be crossed over to receive EMD 1201081 + cetuximab at progression if they desire. Treated subjects will not be replaced.

Intervention

Subjects will be randomized to the two treatment groups at a ratio of 1:1. The Investigational Medicinal Products are EMD 1201081 (formerly known as IMO-2055) and cetuximab (= reference therapy, control arm), which is regarded an IMP outside the US.
EMD 1201081 (0.32 mg/kg) will be administered subcutaneously once a week. Subjects may dose-reduce to alleviate side-effects if they still could benefit from trial participation.
For the purposes of this trial, a cycle is defined as 3 weeks (21 days).

Study burden and risks

EMD 1201081 frequently causes local reactions at the injection site (e.g. redness, swelling pain), nausea and vomiting. Cetuximab frequently causes skin reactions (e.g. acne-like rash) and nail disorders (pain, tenderness and cracking of finger and toenails). An extensive list of side effects, including those occurring less frequently, is taken up in appendix 2 of the subject information. There may also be side effects associated with EMD 1201081 and/or

the combined treatment with cetuximab that are not yet known.

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

1. Signed and dated written informed consent prior to any trial-specific procedure.
2. Male or female, age >= 18 years.
3. Histologically confirmed squamous cell carcinoma of the head and neck that is recurrent and/or metastatic documented in the medical record.
4. History of progressing disease on a first-line cytotoxic chemotherapy regimen such as 5-FU + cisplatin, taxanes, etc. for their R/M SCCHN. (A history of chemotherapy/ radiation therapy for localized disease does not count as a first-line regimen.)
5. The subject is suited for systemic therapy in the opinion of the Investigator.
6. At least one radiographically documented lesion assessable according to RECIST 1.0.

Lesions in previously irradiated areas should be measurable (i.e. the lesion must be adequately measurable in at least one dimension; longest diameter to be recorded as >= 2 cm by conventional techniques or >= 1 cm by spiral CT scan). If the sole site of measurable disease is in a prior radiation field, there must be unequivocal evidence of progression at >= 8 weeks since the
completion of radiation or a positive biopsy.
7. ECOG performance status of 0 or 1.
8. If female, either post-menopausal, surgically sterile, or having a negative urine or serum pregnancy test (β-HCG) at screening and practicing medically accepted contraception. If male, practicing contraception if risk of conception exists. For relevant subjects, the duration of contraception should be 1 week prior to the start of therapy through 4 weeks after receipt of trial therapy.
9. Recovered from previous toxicities of prior cytotoxic regimen to CTCAE Grade 1 (with the exception of alopecia).
10. Hemoglobin >= 9 g/dL (without transfusion support, no transfusion within 7 days of screening).
11. Neutrophils >= 1.5 x 109/L.
12. Platelets >= 100 x 109/L.
13. PT/PTT <= 1.5 times the upper limit of normal for the site, unless there is therapeutic anti-coagulation (see below; INR values should be converted to PT for screening).
14. Serum creatinine <= 1.5 times the upper limit of normal for the site.
15. ALT and AST <= 3 times the upper limit of normal for the site.
16. Be willing and able to comply with the protocol procedures for the duration of the trial.

Exclusion criteria

1. History of prior exposure to cetuximab or panitumumab or any other approved or investigational
anti-EGFR agents.
2. Undifferentiated nasopharyngeal carcinoma.
3. Chemotherapy, radiotherapy or any investigational agents within 4 weeks of first dose of trial medication.
4. Major surgical or planned procedure within 30 days prior to first dose of trial medication (isolated biopsies are not counted as major surgical procedures).
5. Other active malignancy (other than SCCHN) besides non-metastatic basal cell or squamous cell carcinoma of the skin or second primary squamous cell carcinoma of the head and neck.
6. Impaired cardiac function (e.g. left ventricular ejection fraction < 45% defined by echocardiograph or other study), history of uncontrolled serious arrhythmia, unstable angina pectoris, congestive heart failure (NYHA III and IV), myocardial infarction within the last 12 months prior to trial entry, signs of pericardial effusion.
7. Hypertension uncontrolled by standard pharmacologic therapies.
8. History of diagnosed interstitial lung disease.
9. Patient requires systemic anti-coagulation (e.g. warfarin > 10 mg/day).
10. Pregnancy or breast feeding.

11. Legal incapacity or limited legal capacity.
12. Significant medical or psychiatric disease which makes the trial inappropriate for the subject in the Investigator*s opinion.
13. Any brain metastasis and/or leptomeningeal disease (known or suspected).
14. Significant pre-existing immune deficiency such as infection by HIV (documented or known).
15. Clinically significant ongoing infection.
16. Known hypersensitivity to the trial treatments.
17. Participation in another clinical trial within the past 30 days.
18. Signs and symptoms suggestive of transmissible spongiform encephalopathy, or family members who suffer(ed) from such.
19. Other significant disease that in the Investigator*s opinion would exclude the subject from the trial.

Study design

Design

Study phase:	2
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):	01-04-2011
Enrollment:	20
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Cetuximab
Generic name:	Erbitux

Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	EMD 1201081

Ethics review

Approved WMO Date:	20-01-2011
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	01-06-2011
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	EUCTR2009-014440-10-NL
ClinicalTrials.gov	NCT01040832
CCMO	NL35338.068.11