An Open Label, Randomized Phase 3 Clinical Trial of Nivolumab vs Therapy of Investigator's Choice in Recurrent or Metastatic Platinum-refractory Squamous Cell Carcinoma of the Head and Neck (SCCHN)

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The study will look at patients with Squamous Cell Head and Neck Cancer (SCCHN) whose tumours express a certain type of protein called PD-L1. The research aims to compare a new drug called nivolumab against Investigator's choice of chemotherapy…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON44380

Source
ToetsingOnline

Brief title
CA209-141

Condition

- Other condition

Synonym
HNSCC

Health condition

Squamous Cell Carcinoma of Head and Neck region

Research involving
Human

Sponsors and support

Primary sponsor: Bristol-Myers Squibb
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: HNSCC, Nivolumab, PD-L1

Outcome measures

Primary outcome

To compare PFS and OS of Nivolumab to Investigator*s Choice in subjects who have tumor progression within 6 months of last dose of platinum therapy in the primary, recurrent, or metastatic setting.

Secondary outcome

Secondary Objectives

• To compare Objective Response Rate (ORR) of Nivolumab to Investigator*s Choice.

Exploratory Objectives

• To assess the safety of nivolumab in subjects with SCCHN.

• To estimate Duration of Response (DoR) and Time to Response (TTR) of nivolumab and Investigator*s Choice arms

• To evaluate the pharmacodynamic activity of nivolumab or single agent

chemotherapy on the immune system in the peripheral blood and tumor tissue.

• To investigate the association between biomarkers in the peripheral blood and tumor tissue, such as PD-L1 expression, with safety and efficacy for subjects with advanced or metastatic tumors treated with nivolumab monotherapy.

• To characterize the PK of nivolumab, and to explore exposure-response relationships.

• To characterize the immunogenicity of nivolumab.

• To evaluate health related quality of life using a validated instrument in the European Organisation for Research and Treatment of Care General Cancer Module (QLQ-C30) and head and neck specific module (QLQ-H&N35).

• To evaluate patient reported general health status as assessed by the five item EQ-5D.

Study description

Background summary

Despite the numerous treatment options, metastatic or recurrent Squamous Cell Head and Neck Cancer remains an area of high unmet medical need as patients who progress after treatment (refractory or platinum-resistant disease) have the worst prognosis with median OS of 3 - 4 months and 1 year survival rate of < 5%.20 In conclusion, there is no effective standard of care that provides survival benefits beyond 4 - 6 months in second line platinum refractory recurrent or metastatic Squamous Cell Head and Neck Carcinoma.

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. Nivolumab is a type of immunotherapy drug called a monoclonal antibody. By blocking a protein (called PD-1) in the body, nivolumab helps to stimulate the body*s own immune system to help attack the cancer cells.

Nivolumab has demonstrated clinical activity across several tumor types, including advanced melanoma, NSCLC, and RCC. Nivolumab has demonstrated a

manageable safety profile in > 1,500 subjects across all clinical trials. The AE profile for nivolumab does not appear to be dose dependent and appears to be similar across a range of solid tumours studied.

Preliminary data suggest that PD-L1 tumor expression may be predictive for response to Nivolumab and these receptors are present in Squamous Cells .

BMS would like to evaluate nivolumab in subjects with platinum refractory SCCHN as we believe it could provide further treatment options for patients with a high unmet medical need.

Study objective

The study will look at patients with Squamous Cell Head and Neck Cancer (SCCHN) whose tumours express a certain type of protein called PD-L1. The research aims to compare a new drug called nivolumab against Investigator's choice of chemotherapy to see how this treatment helps patients compared to what is currently used.

BMS believes that, patients who are strongly PD-L1 positive and treated with Nivolumab, could live longer without their disease getting worse, this is known as progression free survival (PFS). It is also believed, and will be measured in the study, that patients Overall Survival (OS) will be increased when recieving Nivolumab treatment.

Study design

Eligable HNNSC patients enrolled into the study, will be randomised to one of two arms,

Arm N: Nivolumab 3 mg/kg IV every 2 weeks

Arm IC: one of the following single agents
- Methotrexate 40 mg/m2 IV push weekly, may be increased to 60 mg/m2 if tolerated as per local practices
- Docetaxel 30 mg/m2 IV weekly, may be increased to 40 mg/m2 if tolerated as per local practice.

Tumor progression or response endpoints will be assessed using a centralized imaging review (IRRC) and UK standard response criteria (RECIST 1.1). Treatment with study medication will continue until RECIST 1.1 defined progression, unacceptable toxicity, or withdrawal of consent.

Dose reductions will be not be allowed for nivolumab. Treatment beyond initial investigator-assessed progression (either clinical or radiographical) is permitted for nivolumab if the subject is believed to have had some clinical

benefit and is tolerating study drug.

A Data Monitoring Committee will be established and meet regularly during the study to ensure that subject safety is carefully monitored and to provide oversight regarding safety and efficacy of the drug.

The total duration of the study from start of randomization to final analysis of PFS is expected to be ~ 26 months, assuming a fixed accrual rate of 10 randomized subjects per month.

The study will end once survival follow-up has concluded, ie the required number of death events have happened.
The last visit will be the last follow-up visit 2 for subjects still on study drug treatment once survival follow-up has concluded; this visit is expected to take place approximately three and a half years after start of randomization.

Intervention

The details of each of the possible treatments and how you may receive them in this study are listed below;

A pump will be used for the intravenous infusions to ensure the correct amount of medicine is given over the proper amount of time.
This study is open label, which means that the subject and investigator will know what drug is being received.

Nivolumab
Administered every 2 weeks by intravenous infusion (IV) - The infusion usually takes about 1 hour (60 minutes)
Patients may also receive additional medication before the study drug infusion to avert side effects or hypersensitivity reactions (allergic reactions)

Docetaxel
Administered every week by intravenous infusion (IV) - 1 hour (60 minutes)
Patients may - if assesed as required by study doctor - have an interruption (or a dosing break) and to skip one dose after every 3 doses
Patients may also receive additional medication before the study drug infusion to avert side effects or allergic reactions

Methotrexate
Administered every week by intravenous infusion (IV) - 1 hour (60 minutes)

Study burden and risks

As part of the trial, patients will be expected to attend multiple clinic

visits, where they will undergo physical examinations, vital sign measurements (including oxygen saturation levels), blood tests for safety assessment, pregnancy testing (for females of child bearing potential), and monitoring for adverse events.

In addition, every 6 weeks (starting at week 9), patients will undergo radiographic assessment of their tumours (by CT or MRI) until disease progression or treatment discontinuation whichever occurs later.

Blood will also be collected at certain visits for research purposes (PK, immunogenicity and biomarker studies). Blood or urine sample for pregnancy testing: Urine or serum pregnancy tests will also be performed where applicable for women of childbearing potential.

The frequency of visits and number of procedures carried out during this trial would typically be considered over and above standard of care.

These procedures are conducted by medically trained professionals and every effort will be made to minimise any risks or discomfort to the patient.

Treatment for cancer often has side effects, including some that are life threatening. An independent Data Monitoring Committee will be utilised to monitor this trial.

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

Inclusion Criteria;1. Signed Written Informed Consent
a) Subjects must have signed and dated an IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol related procedures that are not part of normal subject care.
b) Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory testing, and other requirements of the study.;2. Target Population
a) Histologically confirmed recurrent or metastatic SCCHN (oral cavity, pharynx, larynx), stage III/IV and not amenable to local therapy with curative intent (surgery or radiation therapy with or without chemotherapy).
b) Eastern Cooperative Oncology Group (ECOG) performance status of 0-1 (Refer to Appendix 1).
c) Documentation of p16-positive or p16-negative disease to determine human papillomavirus (HPV) status of tumor for NSCC of the oropharynx.
d) Tumor progression or recurrence within 6 months of last dose of platinum therapy in the adjuvant (ie with radiation after surgery), primary (i.e., with radiation), recurrent, or metastatic setting. Clinical progression after platinum therapy is an allowable event for entry and is defined as progression of a lesion at least 10 mm in size that is amenable to caliper measurement (e.g. superficial skin lesion as per RECIST 1.1) or a lesion that has been visualized and photographically recorded with measurements and shown to have progressed.
e) Measurable disease by CT or MRI per RECIST 1.1 criteria (Appendix 3).
f) Tumor tissue (archival or fresh biopsy specimen) must be available for PD-L1 expression analysis and other biomarker correlative studies. For subjects where a fresh biopsy is not feasible, archival tumor material must be made available. The subject must not have received systemic therapy subsequent to obtaining the archived biopsy and prior to screening. Tumor tissue must have been obtained in the metastatic setting or from an unresectable site of disease. For more details, see Section 5.7.3
g) Prior curative radiation therapy must have been completed at least 4 weeks prior to study drug administration. Prior focal palliative radiotherapy must have been completed at least 2 weeks before study drug administration.
h) Immunosuppressive doses of systemic medication, such as steroids or absorbed topical steroids (doses > 10 mg/day prednisone or equivalent) must be discontinued at least 2 weeks before study drug administration.

i) Screening laboratory values must meet the following criteria (using CTCAE v4) and should be obtained within 14 days prior to randomization:
i) WBC >=2000/µL
ii) Neutrophils >= 1500/µL
iii) Platelets >= 100 x103/µL
iv) Hemoglobin >= 9.0 g/dL
v) Serum creatinine >= 1.5 x ULN or creatinine clearance (CrCl) > 40 mL/min (using the Cockcroft-Gault formula): Female CrCl = (140 - age in years) x weight in kg x 0.85 72 x serum creatinine in mg/dL Male CrCl = (140 - age in years) x weight in kg x 1.00 72 x serum creatinine in mg/dL
vi) AST/ALT <= 3 x ULN
vii)Total Bilirubin <= 1.5 x ULN (except subjects with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL).
viii) Calcium levels must be normalized and maintained within normal limits for study entry and on treatment. Medical management of calcium levels is permitted.
ix) Subjects with an initial magnesium < 0.5 mmol/L (1.2 mg/dL) may receive corrective magnesium supplementation but should continue to receive either prophylactic weekly infusion of magnesium and/or oral magnesium supplementation (e.g. magnesium oxide) at the investigator*s discretion.
j) Subjects must have resting baseline O2 saturation by pulse oximetry of >= 92% at rest.
k) Subject Re-enrollment: This study permits the re-enrollment of a subject that has discontinued the study as a pre-treatment failure (i.e., subject has not been randomized / has not been treated). If re-enrolled, the subject must be re-consented.;3. Age and Reproductive Status
a) Males and Females, >= 18 years of age.
b) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug.
c) Women must not be breastfeeding.
d) WOCBP must agree to follow instructions for method(s) of contraception from the time of enrollment for the duration of treatment with study drug(s) plus 5 half-lives of study drug(s) plus 30 days (duration of ovulatory cycle) for a total of 23 weeks post treatment completion.
e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug(s) plus 5 half-lives of study drug(s) plus 90 days (duration of sperm turnover) for a total of 31 weeks post treatment completion.
f) Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However, they still must undergo pregnancy testing as described in these sections. Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly.
At a minimum, subjects must agree to the use of two methods of contraception, with one method being highly effective and the other method being either highly effective or less effective as listed below:;HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

• Male condoms with spermicide
• Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants, and intrauterine devices (IUDs) such as Mirena by WOCBP subject or male subject*s WOCBP partner.
• Nonhormonal IUDs, such as ParaGard®
• Tubal ligation
• Vasectomy
• Complete Abstinence.*
*Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.;LESS EFFECTIVE METHODS OF CONTRACEPTION
• Diaphragm with spermicide
• Cervical cap with spermicide
• Vaginal sponge
• Male Condom without spermicide
• Progestin only pills by WOCBP subject or male subject*s WOCBP partner
• Female Condom*
*A male and female condom must not be used together.

Exclusion criteria

Exclusion Criteria;1. Target Disease Exceptions
a) Active brain metastases or leptomeningeal metastases are not allowed. Subjects with brain metastases are eligible if these have been treated and there is no magnetic resonance imaging (except where contraindicated in which CT scan is acceptable) evidence of progression for at least 8 weeks after treatment is complete and within 28 days prior to first dose of study drug administration. Cases, including base of skull lesions without definitive evidence of dural or brain parenchymal involvement, should be discussed with the medical monitor. There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration.
b) Histologically confirmed recurrent or metastatic carcinoma of the nasopharynx and salivary gland or non-squamous histologies (e.g. mucosal melanoma) are not allowed.;2. Medical History and Concurrent Diseases
a) Any serious or uncontrolled medical disorder that, in the opinion of the investigator, may increase the risk associated with study participation or study drug administration, impair the ability of the subject to receive protocol therapy, or interfere with the interpretation of study results.
b) Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast.
c) Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, type

I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
d) Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.
e) Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways.
f) All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to Grade 1 (NCI CTCAE version 4) or baseline before administration of study drug. Subjects with toxicities attributed to prior anti-cancer therapy which are not expected to resolve and result in long lasting sequelae, such as neuropathy after platinum based therapy, are permitted to enroll.
g) Treatment with any chemotherapy, radiation therapy, biologics for cancer, or investigational therapy within 28 days of first administration of study treatment (subjects with prior cytotoxic or investigational products < 4 weeks prior to treatment might be eligible after discussion between investigator and sponsor, if toxicities from the prior treatment have been resolved to Grade 1 (NCI CTCAE version 4).;3. Physical and Laboratory Test Findings
a) Positive test for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (HCV antibody) indicating acute or chronic infection.
b) Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).
c) Any Grade 4 laboratory abnormalities.;4. Allergies and Adverse Drug Reaction
a) History of allergy to study drug components.
b) History of severe hypersensitivity reaction to any monoclonal antibody.;5. Other Exclusion Criteria
a) Prisoners or subjects who are involuntarily incarcerated.
b) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.

Study design

Design

Study phase:	3
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):	30-07-2014
Enrollment:	9
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Docetaxel
Generic name:	Taxotere
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Methotrexate
Generic name:	Trexall
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Nivolumab
Generic name:	BMS-936558

Ethics review

Approved WMO Date:	26-06-2014
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	29-07-2014
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	26-09-2014

Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	29-10-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	30-01-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	05-02-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	23-04-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	07-05-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	13-07-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	14-07-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	09-02-2016
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	26-02-2016

Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	22-04-2016
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	28-04-2016
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	EUCTR2013-003622-86-NL
CCMO	NL48720.058.14