A RANDOMIZED DOUBLE-BLIND PHASE 3 STUDY OF AVELUMAB IN COMBINATION WITH STANDARD OF CARE CHEMORADIOTHERAPY (CISPLATIN PLUS DEFINITIVE RADIATION THERAPY) VERSUS STANDARD OF CARE CHEMORADIOTHERAPY IN THE FRONT LINE TREATMENT OF PATIENTS WITH LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

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To demonstrate that treatment with avelumab in combination with standard of care (SOC) CRT is superior to SOC CRT alone in prolonging progression-free survival (PFS) in front-line patients with high-risk (as defined in Inclusion Criterion 2),...

Ethical review	Not approved
Status	Will not start
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON45350

Source
ToetsingOnline

Brief title
B9991016 - JAVELIN HEAD AND NECK 100

Condition

- Other condition
- Miscellaneous and site unspecified neoplasms benign

Synonym
Squamous cell carcinomas of the head and neck (SCCHN) ; Head and neck cancers

Health condition

Squamous cell carcinomas of the head and neck (SCCHN)

Research involving
Human

Sponsors and support

Primary sponsor: Pfizer
Source(s) of monetary or material Support: industry

Intervention

Keyword: avelumab, Head and neck cancer, Phase 3, randomized

Outcome measures

Primary outcome

PFS per modified Response Evaluation Criteria in Solid Tumors (RECIST) version

(v)1.1 (see Appendix 3 for specific modifications, including pathologic

confirmation) by investigator assessment

Secondary outcome

* OS.

* Antitumor Activity: Pathologic complete response in any resected specimens,

neck dissection.

* Antitumor Activity: Locoregional failure, objective response, distant

metastatic failure, and duration of response, per modified RECIST v1.1

(Appendix 3) by investigator assessment.

* Safety: Adverse events and laboratory abnormalities as graded by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03; vital signs (blood pressure, pulse rate).

* Pharmacokinetics:

* Maximum concentrations (Cmax) and trough concentrations (Ctrough) for avelumab.

* Area under the concentration-time curve extrapolated to infinity (AUCinf), Cmax, clearance (CL), time to maximum plasma concentration (Tmax), elimination half-life (t1/2), and volume of distribution (Vz) for cisplatin (total and free), as data permit.

* Immunogenicity: Incidence of ADA (neutralizing antibody) against avelumab.

* Patient-Reported Outcomes: Disease-related symptoms and Health-Related Quality of Life as measured by the National Cancer Comprehensive Network (NCCN) Head and Neck Symptom Index-22 items (FHNSI-22), and the EuroQoL Group 5-Dimension 5 Level Self-Report Questionnaire (EQ-5D-5L).

* Biomarkers: Tumor tissue biomarkers including, but not limited to, PD-L1 expression and tumor-infiltrating CD8+ T-lymphocytes.

Study description

Background summary

Of newly diagnosed patients with SCCHN, approximately 60% present with locally or regionally advanced disease.Depending on the tumor site, stage, and resectability, locoregional failure rates can range between 35% and 65%. With a median PFS of 1.9 years and reported 3-year PFS rate of 61.2%, this disease will ultimately recur locally in a large proportion of treated patients, with distant metastases developing in 10% to 30% of these patients. Currently

available treatment options for both locoregional and distant recurrences are limited. Outcomes for both groups of recurrences are abysmal, and the limited number of patients who are eligible for potentially curative treatment for locoregional disease recurrence are exposed to a high degree of morbidity.

Study objective

To demonstrate that treatment with avelumab in combination with standard of care (SOC) CRT is superior to SOC CRT alone in prolonging progression-free survival (PFS) in front-line patients with high-risk (as defined in Inclusion Criterion 2), locally advanced SCCHN who are candidates for definitive CRT with cisplatin.

Study design

This is a Phase 3, international, multicenter, randomized, double blind, parallel, 2 arm study. Subjects will be randomized in a 1:1 ratio to either Arm A (avelumab + SOC CRT) or Arm B (placebo + SOC CRT). Randomization will be stratified by tumor (T) stage (N2c/N3), and HPV status (positive vs negative) as measured by p16 expression by
IHC.

Intervention

There will be 3 treatment phases in this study:
* Lead-in Phase: On Day 1 of the Lead-in Phase of the study, patients will receive a single dose of avelumab or matching placebo, administered 7 days prior to initiation of the CRT Phase;
* CRT Phase: Avelumab or matching placebo will be administered on Days 8, 25, and 39 in conjunction with SOC CRT starting on Day 1 of the CRT phase;
* Maintenance Phase: Following completion of the CRT Phase, avelumab or matching placebo will be administered every 2 weeks (Q2W) for 12 months during the Maintenance Phase.

Study burden and risks

During the study the patient has to come about 40 times to the clinic. During these visit a physical examniation is done and blood will be taken. In addition the subject meeds to complete some questionnaires.

Potenital side effects are listed in the investigators Brochure and are summarized in the patient information sheet.

Given the distinct safety profile and mostly non-overlapping toxicities, no significant increased risk is anticipated from the combination of avelumab with CRT including cisplatin for the treatment of locally-advanced SCCHN. The

potential for benefit is significant given the strong preclinical interaction between radiation and immune checkpoint inhibitors as well as the data showing activity as single agents, which in the frontline setting could result in enhanced localregional tumor control and improved PFS and OS. As described previously, treatment options for patients with recurrent SCCHN are limited and associated with severe toxicities; response rates are low, ranging between 15% and 36% with a median OS of 6 to 10.1 months. Improved treatment for locally-advanced, high-risk SCCHN to prevent locoregional relapse and distant metastases is critical for successful management of this multidimensional disease and therefore testing of multimodality therapy is appropriate with an acceptable risk-benefit profile for patients.

The Sponsor plans to closely monitor the safety profile for new emerging safety risks or increased frequency or severity of anticipated risks based on a review of aggregate data.

Contacts

Public
Pfizer

East 42nd Street 235
New York NY 10017
US
Scientific
Pfizer

East 42nd Street 235
New York NY 10017
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

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

Inclusion criteria

1. Histological diagnosis of squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx with tissue available.
2. High-risk disease as defined by:
* HPV negative disease, Stage III, IVa, IVb per tumor/nodes/metastasis (TNM) guidelines for head and neck sites (American Joint Committee on Cancer [AJCC] 7th Edition); or
* Non oropharyngeal HPV positive disease, Stage III, IVa, IVb per TNM guidelines for head and neck sites (AJCC 7th Edition); or
* HPV positive oropharyngeal disease T4, N2c, or N3 per TNM guidelines for head and neck sites (AJCC 7th Edition);
* where HPV status will be determined per institutional standard using p16 immunohistochemistry (IHC).
3. No prior therapy for advanced stage SCCHN; eligible for definitive CRT with curative intent.
4. Available tumor samples for submission or willing to undergo further tumor biopsies:
* Availability of a formalin-fixed paraffin-embedded (FFPE) tumor tissue block from primary tumor or nodal biopsy. If an FFPE tissue block cannot be provided, 15 unstained slides (10 minimum) will be acceptable.
5. Age *18 years (*20 years in Japan).
6. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 or 1.
7. Adequate bone marrow function, including:
* Absolute Neutrophil Count (ANC) *1,800/µL or *1.8 x 10E9/L.
* Platelets *100,000/µL or *100 x 10E9/L.
* Hemoglobin *9 g/dL (may have been transfused).
8. Adequate renal function, including:
* Estimated creatinine clearance *50 mL/min as calculated using the Cockcroft Gault (CG) equation.
9. Adequate liver function, including:
* Total serum bilirubin *1.5 x upper limit of normal (ULN).
* Aspartate and alanine aminotransferase (AST and ALT) *2.5 x ULN.
10. Pregnancy test (for patients of childbearing potential) negative at screening.
11. Male patients able to father children and female patients of childbearing potential and at risk for pregnancy must agree to use two highly effective methods of contraception throughout the study and for at least 6 months after the last dose of cisplatin and 60 days after the last dose of avelumab/placebo (whichever is later).
Female patients who are not of childbearing potential (ie, meet at least one of the following criteria):
a. Have undergone a documented hysterectomy and/or bilateral oophorectomy; or b) Have medically confirmed ovarian failure; or Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause and have a serum follicle-stimulating hormone (FSH) level confirming the post-menopausal state.
12. Evidence of a signed and dated informed consent document indicating that the patient

(or a legally acceptable representative, as allowed by local guideline/practice) has been informed of all pertinent aspects of the study.
13.Patients who are willing and able to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures.

Exclusion criteria

1. Prior immunotherapy with an anti PD 1, anti PD L1, anti PD L2, anti CD137, or anti CTLA 4 antibody (including ipilimumab), or any other antibody or drug specifically targeting T cell co stimulation or immune checkpoint pathways.
2. Major surgery * 4 weeks prior to randomization.
3. Diagnosis of any other malignancy within 5 years prior to randomization, except for superficial esophageal cancer (TIS or T1a) fully resected by endoscopy, prostate cancer (Gleason score *6) either curatively treated or deemed to not require treatment, ductal in situ carcinoma of the breast that has completed curative treatment, adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the cervix or bladder.
4. Active autoimmune disease that might deteriorate when receiving an immunostimulatory agent. Patients with diabetes type I, vitiligo, psoriasis, or hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible.
5. Any of the following in the 6 months prior to randomization: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident, transient ischemic attack, or symptomatic pulmonary embolism.
6. Active infection requiring systemic therapy.
7. Known prior severe hypersensitivity to investigational products or any component in the formulations, including known severe hypersensitivity reactions to mAbs, cisplatin, or platinum-related compounds (NCI CTCAE v4.03 Grade * 3).
8. Use of immunosuppressive medication at time of randomization, except the following:
a. Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection);
b. Systemic corticosteroids at physiologic doses *10 mg/day of prednisone or equivalent;
c. Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication).
9. Prior organ transplantation including allogenic stem-cell transplantation.
10. Diagnosis of prior immunodeficiency or known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) related illness.
11. Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection at screening (positive HBV surface antigen or HCV RNA [ribonucleic acid] if anti-HCV antibody screening test positive).
12. Vaccination within 4 weeks prior to randomization except for administration of inactivated vaccines.
13. Current use of or anticipated need for treatment with other anti-cancer drugs.
14. Pregnant female patients, breastfeeding female patients, and male patients able to father children and female patients of childbearing potential who are unwilling or unable to use 2 highly effective methods of contraception as outlined in the protocol for the duration of the study and for at least 6 months after the last dose of cisplatin and 60 days after the last dose of avelumab/placebo (whichever is later).
15. Other severe acute or chronic medical conditions including: colitis, inflammatory bowel

disease, pneumonitis, pulmonary fibrosis, or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior; or laboratory abnormality that may increase the risk associated with study participation or study treatment administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.
16. Patients who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or patients who are Pfizer employees directly involved in the conduct of the study.
17. Participation in other interventional studies involving investigational drug(s) within 4 weeks prior to randomization.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	4
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	N/A
Generic name:	avelumab

Ethics review

Approved WMO Date:	28-03-2017
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Not approved Date:	27-07-2017
Application type:	First submission
Review commission:	METC Brabant (Tilburg)

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	EUCTR2016-001456-21-NL
ClinicalTrials.gov	NCT02952586
CCMO	NL60707.028.17