Single-arm, multicenter, phase II study of immunotherapy in patients with type B3 thymoma and thymic carcinoma previously treated with chemotherapy - (Nivothym)

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This study has been transitioned to CTIS with ID 2023-508658-24-00 check the CTIS register for the current data. Main objective: To assess PFS rate at 6 months in patients treated with nivolumab or the combination of nivolumab and ipilimumab, with...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Respiratory and mediastinal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON55734

Source
ToetsingOnline

Brief title
Nivothym

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
Thymoma and thymic carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: European Organisation for Research in Treatment of Cancer (EORTC)
Source(s) of monetary or material Support: European Organisation for Research and Treatment of Cancer

Intervention

Keyword: Immunotherapy, thymic carcinoma, type B3 thymoma

Outcome measures

Primary outcome

Progression Free Survival Rate at 6 months (PFS-6) per independent radiological

review (BICR) based on RECIST 1.1.

Secondary outcome

- Progression Free Survival Rate at 6 months (PFS-6) according to RECIST 1.1

per local investigator assessment.

- Safety according to CTCAE v4.0;

- Overall Response Rate (ORR) according to RECIST 1.1 per local investigator

assessment ;

- Disease Control Rate according to RECIST 1.1 per local investigator

assessment (DCR);

- Duration of response according to RECIST 1.1 per local investigator

assessment;

- Progression Free Survival (PFS) according to RECIST 1.1 per local

investigator assessment;

- Overall Survival (OS).

- Progression Free Survival for patients continuing treatment after

progression.

Study description

Background summary

The management of type B3 thymoma and advanced thymic carcinoma remains challenging given the limited amount of evidence in the available literature. After first-line chemotherapy usually incorporating anthracyclines, cisplatin, and/or etoposide and/or taxanes, no second-line option has been established. Sunitinib has been recently evaluated in a phase II trial, that demonstrated limited efficacy in terms of response and disease control rate in thymic epithelial tumors, including thymic carcinomas (ORR 26%, PFS 7,3 months). Other options include the off-label use of pemetrexed, etoposide, or gemcitabine with no reported series to assess their efficacy.
Immunotherapy using PD-1 inhibitors represents a new avenue in the treatment of aggressive cancers in adults, including squamous cell lung cancer, providing patients with the opportunity of long-term survival with limited toxicity.
Thymic carcinoma is a good candidate to assess the efficacy of such strategy given 1) the histologic subtype, mostly consisting of squamous cells, 2) the frequent expression of PD-L1, as
discussed above, and 3) the high rate of genomic aberration, a criteria previously reported to predict durable benefit of immunotherapy.

Study objective

This study has been transitioned to CTIS with ID 2023-508658-24-00 check the CTIS register for the current data.

Main objective:
To assess PFS rate at 6 months in patients treated with nivolumab or the combination of nivolumab and ipilimumab, with relapsed/advanced thymic carcinoma and type B3 thymoma not amenable to curative-intent radical treatment and previously treated with platinum-based chemotherapy

Secondary objectives:
- To assess Overall Response Rate (ORR), Disease Control Rate (DCR) and duration of response of nivolumab or nivolumab in combination with ipilimumab;
- To assess OS and PFS;
- To assess the safety of nivolumab or nivolumab in combination with ipilimumab in this study population.

Study design

This is a 2 cohort phase II, multicenter, single arm study assessing the activity and safety of nivolumab or in combination with ipilimumab in advanced/metastatic patients with type B3 thymoma and thymic carcinoma that have received a first line platinum-based chemotherapy.

Intervention

Cohort 1: Nivolumab monotherapy
Nivolumab 240 mg IV every 2 weeks, continued until PD, unacceptable toxicity, patient refusal or death.

Patients who receive nivolumab and will not be progressing after 1 year of treatment are allowed to interrupt nivolumab administration. If progression occurs and patients fullfill all criteria for nivolumab administration, they will have the opportunity to resume nivolumab until PD as per investigator decision.

Cohort 2: Nivolumab and Ipilimumab
Nivolumab administered IV over 30 minutes 240 mg every 2 weeks Ipilimumab administered IV over 30 minutes at 1 mg/kg every 6 weeks.
On the day of infusion, nivolumab is to be administered first. The second infusion will always be ipilimumab, and will start at least 30 minutes after completion of the nivolumab infusion. Both drugs will be administered until progression, unacceptable toxicity, or other reasons.

Patients that receive nivolumab and ipilimumab and will not be progressing after 1 year of treatment will be allowed to interrupt nivolumab and ipilimumab administration. If progression occurs and patients fullfill all criteria for nivolumab and ipilimumab administration, they will have the opportunity to resume nivolumab and ipilimumab until PD.

Study burden and risks

An ECG will be done at screening. Nivolumab (with or without Ipilimumab) is given every 2 weeks, so physical examination and lab. tests will also be done every 2 weeks (Ipilimumab will be given every 6 weeks). Tumor assessment by CT-scan will be done at week 8 and every 6 weeks thereafter, so this is according to the standard. At baseline, FFPE tissue (archival allowed) will be collected for mandatory translational research as well as blood samples at three timepoints and a fresh frozen tissue sample (biopsy) for optional TRs. The risk of participation in this study is that there will be more blood taken than normally and a fresh frozen tumor tissue sample (biopsy) for TR (optional). A biopsy possibly may cause a bleeding, low blood pressure, redness, bruising, swelling and/or infection at the site of biopsy or other discomfort, such as fair feeling. The anesthetic can possibly give an allergic

reaction. On the place where the biopsy has been done, a scar can arise. If a tumor in the lung is punctured a pneumothorax can occur.
All the patients get nivolumab with or without ipilimumab and may experience specific side effects of nivolumab and ipilimumab.

Contacts

Public
European Organisation for Research in Treatment of Cancer (EORTC)

Avenue E. Mounier 83/11
Brussels 1200
BE
Scientific
European Organisation for Research in Treatment of Cancer (EORTC)

Avenue E. Mounier 83/11
Brussels 1200
BE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

*Relapsed/advanced thymoma B3 or thymic carcinoma not amenable to curative-intent radical treatment; *At least one previous line of platinum-based chemotherapy for advanced disease - Patients treated with neo-adjuvant or adjuvant platinum-based chemotherapy combined with radical surgery or as part of radical chemoradiotherapy are eligible if chemotherapy was completed less than 6 months before enrollment; *Radiological progression

documented per RECIST 1.1 during or after completion of previous line therapy; *Presence of measurable disease according to RECIST 1.1.; -Disease status must be documented by full chest and upper abdomen (including adrenal glands) CT and/or MRI and brain CT and/or MRI within 28 days prior study enrollment. *At least 18 years; *WHO Performance Status (PS) 0-2; *Availability of FFPE tumor tissue (preferentially a tumor block or 10 unstained slides), notably for PD-L1 immunohistochemistry (IHC) expression assessment. Archival material is allowed. Tissue must be considered adequate (assessed by a local pathologist) for characterization of PD-L1 status as per procedure manual; *Adequate hematological function: -White blood count >= 2 × 109/L; -Haemoglobin >9 g/dL; -Platelet count >100 × 109/L; *Adequate liver function: -Total bilirubin <1.5 × ULN (except subjects with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL); -LT and/or AST <2.5 × ULN (< 4 x ULN in case of liver metastasis) -Alkaline phosphatase <5 × ULN; *Adequate renal function: calculated creatinine clearance >=50 mL/min (according to Cockroft-Gault, see below); -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; *Women of child bearing potential (WOCBP) must have a negative serum pregnancy test within 72 hours prior to the first dose of study treatment; -Note: women of childbearing potential are defined as premenopausal females capable of becoming pregnant (i.e. females who have had any evidence of menses in the past 12 months, with the exception of those who had prior hysterectomy). However, women who have been amenorrheic for 12 or more months are still considered to be of childbearing potential if the amenorrhea is possibly due to prior chemotherapy, antiestrogens, low body weight, ovarian suppression or other reasons; *Patients of childbearing / reproductive potential should use adequate birth control measures, as defined by the investigator, during the study treatment period and for at least 5 months for a woman and 7 months for a man after the last study treatment. Note:A highly effective method of birth control is defined as a method which results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly. Such methods include: -Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal) -Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable) -Intrauterine device (IUD) -Intrauterine hormone-releasing system (IUS) -Bilateral tubal occlusion -Vasectomized partner -Sexual abstinence (sexual abstinence is only acceptable if this is in line with the preferred and usual lifestyle of the patient) Acceptable birth control methods that result in a failure rate of more than 1% per year include: -Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action -Male or female condom with or without spermicide -Cap, diaphragm or sponge with spermicide A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods *Female patients who are breast feeding should discontinue nursing prior to the first dose of study medication and must not breast feed during the trial treatment and for a period of at least 5 months

following the last administration of trial drug(s); *Before patient registration, written informed consent must be given according to ICH/GCP, and national/local regulations.

Exclusion criteria

*Any evidence of active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided they are clinically stable (i.e. without evidence of progression by imaging for at least four weeks prior to enrollment and any neurologic symptoms have returned to baseline), and have not received steroids (for a total equivalent dose of more than 10 mg of prednisone per day) for at least 7 days prior to enrollment; *Prior treatment with anti-PD-1, anti-PD-L1/2, anti-CD137, CTLA-4 modulators; *Presence of acetylcholine receptor antibodies; *Current participation in any other clinical research or treatment with an investigational agent or use of an investigational device within 4 weeks of enrollment; *Known active Hepatitis B (e.g., positive HBsAg result) or C (e.g., HCV RNA[qualitative] is detected) or known history or current evidence of Human Immunodeficiency Virus (HIV) (HIV-1/2 antibodies); *If CT has to be used, known contra-indications for CT with IV contrast; *Chronic use of immunosuppressive agents and/or systemic corticosteroids or any use in the last 15 days prior to enrollment; -Corticosteroid use as premedication for IV contrast allergies/reactions is allowed; -Daily prednisone at doses up to 10 mg or equivalent doses of any other corticosteroid is allowed for example as replacement therapy; *History of interstitial lung disease (ILD) OR pneumonitis (other than COPD exacerbation) that has required oral or IV steroids; *Active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (i.e., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment and is allowed; *Live vaccines within 30 days prior to the first dose of study therapy and while participating in study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, H1N1 flu, rabies, BCG, and typhoid vaccine. *Autoimmune paraneoplastic syndrome requiring immunosuppressive or dedicated treatment. Particular attention should be given to detecting any minor myasthenia signs or positive autoantibodies at enrollment; *History of any other hematologic or primary solid tumor malignancy, unless in remission for at least 5 years. pT1-2 prostatic cancer Gleason score < 6, superficial bladder cancer, non melanomatous skin cancer or carcinoma in situ of the cervix are allowed; *Previous allogeneic tissue/solid organ transplant; *Active infection requiring therapy; *Surgery or chemotherapy related toxicity that have not resolved to a grade 1, with the exception of alopecia, fatigue, neuropathy and lack of appetite /nausea; *Severe comorbidities that in the opinion of the investigator

might hamper participation to the study and/or treatment administration; *Any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	05-04-2019
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Nivolumab
Generic name:	Nivolumab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Yervoy
Generic name:	Ipilimumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	15-05-2018
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	04-02-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	12-03-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-03-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-05-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-07-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-06-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-06-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	03-01-2023

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-09-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	21-02-2024
Application type:	Amendment
Review commission:	METC NedMec

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
EU-CTR	CTIS2023-508658-24-00
EudraCT	EUCTR2015-005504-28-NL
CCMO	NL65081.031.18