Ipilimumab plus Nivolumab and ChemoRadiotherapy followed by Surgery in patients with resectable and borderline resectable T3-4N0-1 NSCLC

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Primary objective:• To assess the safety and feasibility of adding ipilimumab-nivolumab to a CRT induction protocol• To assess the efficacy of adding ipilimumab-nivolumab to CRT on the likelihood of a pCR and MPRSecondary objectives: • Local and...

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

Summary

ID

NL-OMON48462

Source
ToetsingOnline

Brief title
INCREASE

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified
- Respiratory tract neoplasms

Synonym
lung cancer, lung carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: BMS (producent van ipilimumab en nivolumab),Bristol-Myers Squibb

Intervention

Keyword: chemoradiotherapy, immunotherapy, NSCLC, surgery

Outcome measures

Primary outcome

Safety defined as (i) the percentage of patients with adverse events (NCI CTCAE), and with each adverse event, the grade and the relationship to ipi/nivo will be assessed, and (ii) complications that lead to delays in administering CRT, or to cancellation of surgery, as well as the rates of post-surgical morbidity. Pathologic complete responses, as well as the percentage of viable tumor in other cases, will be assessed on all the resection specimens.

Secondary outcome

Clinical outcome parameters such as time to local or distant recurrence, and OS at 1 and 2 years will be registered.

Study description

Background summary

Chemoradiotherapy (CRT) can destroy tumor cells both locally and systemically by exerting direct toxic effects, and to some extent, also by boosting anti-cancer immunity. We hypothesized that adding ipilimumab/nivolumab during CRT will act synergistically by further enhancing immune activation, thereby leading to better local and distant tumor control in patients with NSCLC. In this study, we aim to prove that in patients with large tumors, or tumors invading adjacent organs, the addition of ipilimumab-nivolumab (IPI/NIVO) to standard induction CRT is safe, and that it could increase the incidence of

pathologic complete responses (pCR) and major pathologic response (MPR), and eventually improve disease free and overall survival.

Study objective

Primary objective:
• To assess the safety and feasibility of adding ipilimumab-nivolumab to a CRT induction protocol
• To assess the efficacy of adding ipilimumab-nivolumab to CRT on the likelihood of a pCR and MPR
Secondary objectives:
• Local and distant recurrence rates, disease free survival (DFS)
• Overall survival (OS) at 1 and 2 years

Study design

a single center, single arm, phase 1 / 2 trial

Intervention

all patients will be treated with chemoradiotherapy according to international guidelines. In addition, 1 cycle of IPI/NIVO will be administered at the start of radiotherapy and 1 cycle of nivolumab alone will be administered 3 weeks after start of radiotherapy.

Study burden and risks

The burden and risks associated with participation are considered low. The combination of nivolumab concurrent with CRT was proven to be safe. The safety of the combination of concomitant IPI/NIVO and CRT is unknown, however, preliminary safety data on IPI/NIVO consolidation after CRT showed that toxicities were manageable. Neo-adjuvant trials combining chemo and immunotherapy have already shown substantial increases in rates of pCR and MPR. Therefore, we expect patients to draw clinical benefit from participating in this study, particularly as most disease recurrences following trimodality therapy are out-of-field distant metastases. In this trial, the immunological synergy is potentially even higher, as anti-CTLA4 and radiotherapy can prime and activate the effector T-cells. The insights obtained in the translational part of this study can be of high interest for future cohorts of NSCLC patients. Blood withdrawal is considered as a safe procedure.

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. Histologically confirmed NSCLC, a histological biopsy is mandatory
2. T3-4, N0-1 tumors based on size or upon ingrowth into the thoracic wall, mediastinum, vertebra or diaphragm
3. Patients that are irresectable upfront, but expected to be resectable after chemoradiotherapy induction, as per multidisciplinary tumor board evaluation
4. Be willing and able to provide written informed consent for the trial.
5. Be above 18 years of age on day of signing informed consent.
6. Have measurable disease based on RECIST 1.1. 9.
7. Have a performance status of 0-1 on the ECOG Performance Scale.
8. Demonstrate adequate organ function.

Exclusion criteria

1. Known oncogenic drivers such as activating EGFR or BRAF mutations or ALK or ROS1 gene rearrangements

2. Prior surgery and/or radiotherapy on the ipsilateral thorax
3. Patients deemed inoperable
4. Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of day 0. Inhaled or topical steroids, and adrenal replacement steroid >10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
5. Additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.
6. Active autoimmune disease requiring systemic steroid treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids.
7. Evidence of interstitial lung disease or active, non-infectious pneumonitis.
8. Active infection requiring systemic therapy.
9. Ahistory of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
10. Active Hepatitis B or C.
11. Psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
12. Has received prior therapy 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.
13. Patient is pregnant or breastfeeding, or expecting to conceive within the projected duration of the trial, starting with the pre-screening or screening visit through 23 weeks after the last dose of trial treatment.
A Woman of Childbearing Potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes.
WOCBP receiving nivolumab will be instructed to adhere to contraception for a period of 5 months after the last dose of nivolumab. Men receiving nivolumab and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 7 months after the last dose of nivolumab.
These durations have been calculated using the upper limit of the half-life for nivolumab (~25 days) and are based on the recommendation that WOCBP use contraception for 5 half-lives plus 30 days, and men who are sexually active with WOCBP use contraception for 5 half-lives plus 90 days after the last dose of nivolumab. Females should not breastfeed while receiving nivolumab and for any subsequent protocol-specified period. 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. Local laws and regulations may require use of alternative and/or

additional contraception methods. One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as 5 months after the end of study treatment.
HIGHLY EFFECTIVE METHODS OF CONTRACEPTION Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, implantable, or injectable) Hormonal methods of contraception including oral contraceptive pills containing a combination of estrogen and progesterone, vaginal ring, injectables, implants, and intrauterine hormone-releasing system (IUS), Bilateral tubal occlusion, Vasectomized partner, NOTE: A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Intrauterine devices (IUDs). Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.It is not necessary to use any other method of contraception when complete abstinence is elected. WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section5. Alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	05-02-2020
Enrollment:	29
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ipilimumab
Generic name:	ipilimumab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Nivolumab
Generic name:	nivolumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	16-12-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-12-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-05-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-05-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2019-003454-83-NL
CCMO	NL71317.029.19