Upfront resection of locally-advanced or cavitating NSCLC followed by chemoradiotherapy (and adjuvant systemic treatment); Phase 1 multicenter study to assess treatment feasibility and safety

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Respiratory tract neoplasms
Study type	Interventional

Summary

ID

NL-OMON53501

Source
ToetsingOnline

Brief title
NVALT32/UPLAN-I TRIAL

Condition

- Respiratory tract neoplasms

Synonym
Non-small cell lung cancer

Research involving

Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: 0

Intervention

Keyword: Feasibility, Large tumor volume, Locally-advanced NSCLC, Upfront surgery

Outcome measures

Primary outcome

Feasibility as assessed by the number of patients completing the predefined

treatment protocol (upfront resection + cCRT)

Secondary outcome

- Safety (according to CTCAE version 5.0)

- Complications (according to the standardized Clavien-Dindo classification of

surgical complications) will be registered

Study description

Background summary

Stage III non-small cell lung cancer (NSCLC) comprises a heterogeneous group of patients resulting in variable prognoses depending on the size and extent of the primary tumor and the degree of lymph node involvement. For resectable stage III NSCLC, induction chemotherapy, radiotherapy or chemoradiotherapy (CRT) followed by a surgical resection has been demonstrated to improve survival in selected patients when compared to treatment with resection alone. The recent introduction of immune checkpoint inhibitors (ICIs) as induction therapy shows encouraging activity and preliminary results and shows a favorable safety profile in patients with resectable early-stage or locally-advanced NSCLC. However, outcomes of overall survival (OS) have yet to be published. Until recently, guideline-recommended treatment of irresectable stage III NSCLC (e.g. multilevel or bulky N2 disease or presence of N3 lymph node metastases) was concurrent (c)CRT. Recently, ICI (durvalumab) was

successfully added to CRT, showing improved progression free survival (PFS) and OS, now being the standard of care (SoC) treatment for these tumors. So, in stage III NSCLC, possible resectability influences the treatment strategy, however the definition of resectability is subject of discussion and varies between different surgeons and multidisciplinary teams. Therefore, the role of surgery remains unclear so far. When compared to small-sized tumors, large volume (>700cc) and/or cavitating lung tumors are less likely to be sterilized by CRT, increasing the local recurrence rate. After CRT, the quality of life (QoL) might be impaired due to extensive and prolonged coughing. Cardiotoxicity might cause problems and lung function might be seriously impaired after CRT for a large tumor, especially in case of a centrally located tumor. Moreover, necrosis and cavitation of the tumor can cause infectious and/or bleeding complications, including potentially fatal pulmonary hemorrhage. It has been suggested that upfront resection of the large tumor in the lung, with postoperative CRT (aiming for the mediastinal lymph node metastases) in patients who have a potentially resectable tumor could be a strategy to prevent complications of tumor cavitation in large volume tumors. Moreover, it has been shown that in highly selected patients diagnosed with stage IIIB NSCLC, surgical resection as part of multimodality therapy might be associated with improved overall survival (OS). Since (chemo)immunotherapy, or targeted therapy in case of presence of a driver mutation, has the potential to control systemic disease, local control of the primary tumor in the lung becomes more important. Upfront resection of a large volume tumor in the lung might be considered to gain this local control. Moreover, it eliminates the need for CRT on the primary tumor in the lung and thus avoids the potentially serious or life-threatening effects of this treatment.

Study objective

The primary aim of the UPLAN-I trial is to evaluate feasibility and safety of upfront resection of large volume or cavitating tumors in the lung (including a hilar and/or mediastinal lymph node dissection if deemed possible by the treating surgeon), followed by cCRT. The treatment protocol is regarded feasible when at least 15 out 20 patients (75%) are able to undergo cCRT without delay (of more than 10 weeks after de MDT). Secondary aims are establishing safety and recording the incidence of complications.

When feasibility and safety are confirmed in this UPLAN-I trial, the role of upfront resection in reducing infectious problems and subsequently improved QoL, in combination with decreasing the risk of a local recurrence and improving OS, are evaluated in the future UPLAN-II trial.

Study design

Multicenter, open label, intervention, feasibility & safety study

Intervention

Upfront resection of the lung tumour

Study burden and risks

A possible risk of the upfront resection is a delayed start of treatment with cCRT, as the resection precedes the start of cCRT and because possible complications of surgery might postpone the start of further treatment. Potential surgical complications include bleeding, wound infections, lung infections or thrombosis. The aim is to start the cCRT within 4-6 weeks after resection. The risk of delayed treatment with cCRT is potentially acceptable, considering that upfront surgery might benefit patients with large volume stage IIIB/IIIC NSCLC. One of the main benefits this treatment strategy may realise, is a decrease in the occurence of necrosis and infection of the large-volume tumor after treatment with cCRT. Furthermore, it is probable that the patients will require less intensive treatment with radiotherapy due to the resected tumour and affected lymph nodes. In conclusion, potential advantages of an upfront resection include improved local control, reduction of radiotherapy treatment volumes and reduction of long-term infectious problems or bleeding complications. These advantageous outcomes possibly outweigh this risk of a delayed start of the SoC treatment.

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

- Histologically confirmed NSCLC
- cT3-4N2 tumors with cavitation of the primary tumor and/or multilevel or bulky N2
- cT3-4N3 tumors
- Male or female aged aged least 18 years
- The patient must have an Eastern Cooperative Oncology Group (ECOG)/WHO performance status of 0 or 1
- A pretreatment PET/CT scan (of the thorax) and an MRI (or CT scan) of the brain is considered standard of care and must be done prior to treatment
- Pathologically proven NSCLC, staged according to the 8th edition of the AJCC Staging Manual, with a clinical indication for concurrent or sequential CRT (according to current guidelines)
- Patients should be able to receive concurrent or sequential chemoradiotherapy
- Patients should be operable to the discretion of the treating pulmonary physician, surgeon and anesthesiologist, based on lung function testing and performance scoring
- EGFR/ALK mutations and never-smokers may be included in the study since endpoints are settled after finishing chemoradiotherapy and before starting adjuvant systemic treatment
- 'Pathologically proven N2 or N3 lymph node metastasis, or a high suspicion of presence of N2 or N3 lymph node metastasis, based on diagnostic tests and the expert opinion formulated in a multidisciplinary team meeting. When the patient is considered for inclusion without pathology proven N2 or N3 lymph node metastasis, it must be decided that CRT and adjuvant systemic treatment is the optimal treatment plan for that patient during the multidisciplinary team meeting

Exclusion criteria

- Pneumonectomy deemed necessary (by the treating surgeon) to achieve a complete resection (R0)

- Sulcus superior tumor with invasion of the thoracic wall
- cT3-4 based on satellite nodus/lesion in the ipsilateral lung
- Patients with a locoregional recurrence or a secondary primary cancer
- Small cell lung cancer or a pulmonary carcinoid tumor
- Patients who are pregnant or breastfeeding
-Irresectable primary lung tumor before the start of treatment. When resectability is questionable based on diagnostic tests, one of the participating centers must be consulted regarding resectability of the tumor before patient inclusion. If irresectability is established during surgery, the treatment will be considered a failure regarding feasibility.
-Patients who underwent prior high-dose radiotherapy, significantly overlapping with the current PTV.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	03-12-2023
Enrollment:	20
Type:	Actual

Ethics review

Approved WMO Date:	20-12-2022
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	05-07-2023

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-04-2024
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
CCMO	NL81135.041.22