Request for participation in a clinical study:

«Is there a survival benefit of adding thoracic radiotherapy to immunotherapy and chemotherapy for patients with extensive stage small-cell lung cancer?»

Background and intent

This is an invitation for you to participate in a clinical study investigating whether adding thoracic radiotherapy to chemo- and immunotherapy will improve survival in patients with extensive stage small-cell lung cancer. You are invited to participate because you have been diagnosed with this disease.

Chemotherapy has been standard treatment for extensive stage small-cell lung cancer for a long time. Recent studies have shown that adding immunotherapy improves survival, but this treatment is currently not available at all public hospitals. In this study, all participants are offered immunotherapy in addition to chemotherapy.

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Not all patients will, however, have an additional effect of immunotherapy. There are reasons to believe that concurrent radiotherapy can enhance the effect of immunotherapy. The rationale for conducting this trial is to investigate whether this is the case.

What does the study involve?

First, you will have to test for viral infections (hepatitis B, C or HIV), perform a pregnancy test (only relevant for women of childbearing age) and check your heart function. If you test positive for any of the viral infections, are pregnant, or suffer from certain heart conditions, you are not eligible for participation in the study.

All study participants will be offered chemo- and immunotherapy. For the remaining study treatment, participants are divided into two groups. One group will receive radiotherapy against tumors in the lungs and thoracic cavity between the second and third course of chemo- and immunotherapy. The second group will receive chemo- and immunotherapy alone. A computer program randomly decides which group you will join and your doctor cannot influence this randomization.

Radiotherapy is administered in ten fractions over two weeks. Many patients with small-cell lung cancer already receives such radiotherapy, but usually due to disease relapse or poor response to chemotherapy. Based on this, we know that most patients tolerate radiotherapy well.

After four courses of chemo- and immunotherapy we will evaluate the effect of the treatment. Patients with a good response might be offered prophylactic radiotherapy to the brain in order to reduce the risk of brain metastases, which is common in small-cell lung cancer. The use of prophylactic radiotherapy varies between hospitals and will be considered by your physician. Brain irradiation is administered in four to ten fractions over two weeks (depending on local routines).

Thereafter you will receive immunotherapy every fourth week for as long as you tolerate and wish to continue treatment, or until a relapse of disease necessitates a change of treatment.

If you choose not to participate in the study, you will be offered standard treatment: four courses of chemotherapy, possibly followed by whole brain irradiation. Thoracic radiotherapy can be considered if you respond poorly to chemo- and immunotherapy or have a relapse.

If you choose to participate in the study, we will collect and register information about you, your disease and your health condition. You will be examined by a physician regularly and asked to complete a questionnaire at certain intervals. We also wish to collect tissue, blood and stool samples for a response evaluation analysis.

You will find detailed information about the study in chapter A of this document.

Potential advantages, disadvantages and serious adverse events

The most obvious advantage of participation is receiving immuntherapy not currently available at all public hospitals.

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We believe that thoracic radiotherapy can enhance the effect of chemo- and immunotherapy, which is the reason for conducting this trial study.

The disadvantages of collecting blood samples are limited to discomfort related to the pinprick, however the samples are usually collected at the same time as standard blood tests and will not entail extra pricks. Tissue samples confirming relapse will only be collected if your physician deems it safe, and only with your consent. Stool samples are collected at home using a kit delivered to you by study personnel.

You will be monitored closely by study personnel, nurses and physicians throughout the study period. Participation in the study does entail more visits and time spent at the hospital than usual.

Chemotherapy, immunotherapy and radiotherapy can lead to side effects, varying from mild (common) to severe (rare). We cannot identify those at risk of experiencing side effects, therefore it is essential that you contact your physician if you experience any discomfort under or after treatment. The most common side effects are described in chapter A.

Voluntary participation

Participating in the study is voluntary. If you wish to participate, please sign the declaration of consent on the last page of this document. You can withdraw your consent at any time, without stating a reason. This will not have any consequences for your further treatment or follow-up.

If you agree to participate in the study, you are entitled to access information registered about you, and to correct any errors in this information. You can also access our safety measures for data management.

If you withdraw your consent, we will not collect further data or material from you. Already collected material and data will not be deleted and will be included in the planned analyses. If you wish to withdraw from the study, please contact study personnel at your hospital (see contact information).

What will happen to your samples and personal information?

Your samples and data will only be used in accordance with the purpose of the study as described above. Collected data and samples are planned used until 2035. Any amendments in use and/or time span must be approved by the regional ethical committee and other relevant authorities.

All data will be processed without name, personal identification number or other directly recognizable information. A code number links you to your data and samples through a list of names, meaning the information is de-identified. Only the project manager and study personnel at sponsor's trial office and your local hospital have access to this list.

Collected data will be electronically stored at a research server with restricted access. They will be deleted 15 years after the final report has been published.

Publishing study results is a necessary part of the research process. Results will therefore be submitted to international medical journals and to health authorities. No individual participant can be identified in the published results.

Approval

The Regional Committee for Medical and Health Research Ethics in Norway has reviewed and approved the trial (reference number 230766).

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In accordance with the General Data Protection Regulation the data manager (NTNU) and the project manager (Bjørn Henning Grønberg) are independently responsible for ensuring that processing of your personal data has a legal basis. This study is permitted by GDPR article 6a, article 9 nr. 2a and your consent.

You have the right to submit a complaint on the processing of your personal data to the .....

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Contact information

If you have any questions regarding the study, it is easiest for you to contact your local physician or study personnel. You can also contact the National Coordinating Investigator, ...

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Further information about the study is found in chapter A.

Further information about biobanking, data privacy, finances and insurance is found in chapter B.

The declaration of consent follows chapter B. Declaration is to be signed by the study participant. Study personnel confirms to have given information about the study.

Chapter A – Further explanation of what the study involves

Treatment of extensive stage small-cell lung cancer

Chemotherapy (carboplatin plus etoposide) has been standard treatment for patients with small-cell lung cancer for more than 20 years. Recent studies have shown that immunotherapy (durvalumab or atezolizumab) administered in addition to chemotherapy improves survival, but not everyone has an effect of this combination, and better treatment is needed. We have reason to believe that combining radiotherapy with chemo- and immunotherapy can improve the effect of the medical therapy, and the aim of this study is to investigate whether this is the case for patients with extended stage small-cell lung cancer.

All participants in the study are offered four courses of chemotherapy, carboplatin plus etoposide, combined with immunotherapy (durvalumab). The chemotherapy is administered three days every third week. On the first day, chemotherapy is administered intravenously (= into a vein), thereafter one tablet is to be taken in the morning and one in the evening. Take the tablets with a glass of water. Your doctor will inform you on how many tablets you should take at each time point. If you forget to take a tablet, or throw them up, please call your doctor for advice.

Immunotherapy is administered intravenously prior to the first day of each course of chemotherapy. When chemotherapy is completed, immunotherapy treatment will continue every fourth week until you experience serious side effects, until you no longer wish to receive immunotherapy or your disease relapses.

The group of patients randomized to receive thoracic radiotherapy will have this treatment between the second and third course of chemo-immunotherapy. One fraction of the radiotherapy is given daily for ten days (five days per week, usually Monday-Friday). Not all hospitals have a radiotherapy department, which means that participating in the study might entail extra trips to your nearest radiotherapy department. It is not always possible to radiate all tumors, and radiation of tumors outside of the lungs and cavity is not a part of this study. Exactly which and how many tumors can be radiated will be assessed by your physician. Several patients diagnosed with small-cell lung cancer receive radiotherapy today, usually due to a relapse or low tolerability of chemotherapy. Thus, we know that patients normally tolerate radiotherapy well. The novel aspect of this study is that radiotherapy is given concurrently with chemotherapy and immunotherapy. The patients in the group not receiving radiotherapy between the second and third course of chemo-immunotherapy, can be offered radiotherapy at a later stage if recommended by the physician in charge.

After completion of the chemo-immunotherapy, we will perform a CT scan to evaluate the effect of the treatment. Patients with good effect will be considered for prophylactic radiotherapy to the brain, which reduces the risk of brain metastases. This treatment will also be administered with ten doses within two weeks (five days per week, usually Monday-Friday), and is normally well tolerated.

As a part of the study, we will collect and register information about you, your disease and health condition. This information is provided by your patient journal and/or your GP. A physician will examine you, and we will perform an echocardiogram, measure your lung function and test your cognitive function. We will perform regular CT scans of your lungs and abdomen, in addition to MRI scans of your brain to assess the extent of disease, effect of the treatment and whether your disease relapses. After discontinuation of study therapy (regardless of reason), all patients are followed with regular controls up to five years. If your experience a disease relapse, your physician will decide on the best course of action.

Both chemotherapy and immunotherapy can be harmful to fetuses. Women with childbearing potential must therefore use birth control during the study period. Additionally, we will perform pregnancy tests every month from start of treatment until three months after completion of study treatment.

During the course of the study, you will be asked to complete questionnaires for assessment of your health condition at regular intervals. These questionnaires will be handed to you by study personnel when you visit the hospital. If you complete the questionnaire at the hospital, we ask that you return it to study personnel. If you complete it at home, we ask you to return it in the attached, prepaid envelope.

We will also collect the rest of the tissue sample that was taken when you were diagnosed with small-cell lung cancer, as well as any new tissue samples taken to confirm relapse. These samples are stored at the pathology department at your hospital. Additionally, we will collect blood samples for research, and ask you to provide stool samples. The samples are to be collected before, during and after treatment, and in case of a relapse. You will be notified prior to the sampling. Collecting these samples is a key part of our study. There are many unknowns in small-cell lung cancer, and by analyzing these samples we hope to learn more about who are at risk for developing small-cell lung cancer, who will have the best treatment effect, the largest risk for developing serious side effects, and the best prognosis.

Common and serious side effects

Common side effects of chemotherapy are anemia, temporarily impaired immune system and bleedings. It is therefore important that you contact your hospital if you feel ill, get a fever or experience unexpected bleedings. Such side effects usually occur 10-12 day after chemotherapy courses are administered, but they can also occur earlier or later. Chemotherapy can also lead to several other side effects. The most important are allergic reactions, nausea, stomach aches, diarrhea, cardiac dysrhythmia, constipations, feeling unwell, tiredness, hair loss, rashes, dyspnea, high or low blood pressure, and disrupted sensitivity in peripheral nerves.

Durvalumab (immunotherapy) can lead to side effects such as diarrhea, bowel infection, listlessness, nausea, low appetite, dyspnea, cough, constipation, vomit, back ache, fever, anemia, joint pains, swellings, headache, pneumonia, hormonal disturbances (high or low metabolism, diabetes, hypopituitarism, adrenal gland failure), inflammation of muscles, lever, heart, kidney or pancreas, rash, itch, bleedings, nerve injuries, allergic reactions and infections.

Radiotherapy can lead to tiredness, cough, dyspnea, throat pains, headache, hair loss and rash.

It is important that you contact your physician if you experience discomfort during or after treatment, as registration of side effects is a central part of the study.

Other information

If you participate in the study, it is important to inform about your participation if you are in contact with other health care personnel than those treating or following you for your lung cancer.

You will be notified as soon as possible if we receive new information that could impact your decision to participate in the study. You will also be notified if a situation occurs that necessitates terminating your participation earlier than planned.

About 300 patients will be included in the study, at hospitals in Norway, Sweden, Denmark, Lithuania, Estonia and the Netherlands.

Chapter B – Data protection, biobanking, finances and insurance

What information about you will be collected?

We will register information about your health condition, comorbidities, which medications you are using, whether you are experiencing side effects of the treatment, and whether you have any afflictions due to your cancer disease. We might need to collect information from your GP or other hospitals if parts of your treatment is conducted elsewhere, if you contact them because of side effects, or to collect information about your medical history. It might also be necessary to collect information from public registries.

Representatives from the study sponsor (NTNU), the National Medicines Agency as well as national and international regulatory authorities might extradite study information and be allowed to inspect relevant parts of your journal. This is to verify that study information corresponds with information in your journal. Anyone granted such access have a duty of confidentiality.

Data sharing

By participating in the study, you consent to the transfer of de-identified data abroad (within EU/EEC) as a part of research and publishing according to the purpose of the study. The code used to identify you and your data will not be extradited, and we have strict procedures for usage of data.

Access rights and data storage

If you agree to participate in the study, you have a right to access your registered data. Further, you have a right to correct any errors in the registrations. If you withdraw from the study, we will not collect further data or material, however we will not delete already collected information or destruct collected material.

Biobanking, management and analysis of tissue-, stool- and blood samples

Samples are collected at start-up of, during and after study treatment. The tissue samples consist of the remainder of the sample taken at diagnosis to confirm small-cell lung cancer, and any tissue samples taken at relapse. The samples are temporarily stored at participating hospitals pending shipment to Biobank1 in Trondheim, the research biobank of the regional health authority of Central Norway. Samples will be stored until analyses are conducted and will only be used as indicated in the study protocol. Any surplus material will be destructed.

Collected material will be analyzed to investigate coherence between different markers in tissue-, stool- or blood samples and the risk for developing small-cell lung cancer, developing symptoms, disease trajectory, effect of treatment, side effects and survival. This includes genetic markers and analyses of DNA both from the patients' normal cells (including your genome) and cancer cells.

To ensure high data quality and good utilization of collected material, comparing or collating results from other studies or biobanks is an option. Because some methods are not established in Norway, we plan to perform some analyses abroad (within EU/EEC) and ask for your consent to this. The

analyses are for research purposes and will not have any consequences for your follow-up or treatment. For this reason, you will not be notified of the results.

Finances
The study is financed by NTNU, The National Program for Clinical Therapy Research in the Specialist Health Service in Norway (KLINBEFORSK) and the pharmaceutical company Astra Zeneca, who is copyright owner of durvalumab. Nor the study management or other participants have financial gain from participating in the study.

Insurance
All patients are insured according to the Product Liability Act covered by your physician's drug insurance, and by national systems for patient injury compensations.

Information about study results
All study participants are entitled to information about study results, which can be provided by contacting triplex@stolav.no. The results will be published in international journals. Description of the study and a summary of results will also be available at www.clinicaltrials.gov.

Consent for study participation

I hereby confirm that I consent to participate in the study and that clinical and personal data and biological material can be used as described in the study protocol

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(Signed by study participant, date)

Confirmation of provided information
I confirm to having informed the participant about the study

(Signed, study role, date)