MARS
Protocol

Multicentre phase III study: Addition of Radiotherapy to Standard medical treatment for stage IV NSCLC

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Principal Investigator

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SPONSOR	Jan Nyman
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PROTOCOL AGREEMENT FORM

I, the undersigned participating physician, have examined this Protocol

Entitled:

Multicentre phase III study: Addition of Radiotherapy to Standard medical treatment for stage IV NSCLC

And I have fully discussed the objectives of this study and the contents of this protocol with the sponsors' representative(s).

I agree to conduct the study according to this protocol and to comply with its requirements, subject to ethical considerations.

I agree to keep confidential the content of this protocol, not to disclose it to any third party and to use it only for the purpose of conducting this study.

PARTICIPATING PHYSICIAN

NAME**:**_____ SIGNATURE**:**_____

DATE: _____

FOR THE PRINCIPAL INVESTIGATOR

NAME: Jan Nyman SIGNATURE:

DATE: _____

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1 STUDY SUMMARY

Title	Multicentre phase III study: Addition of Radiotherapy to Standard medical treatment for stage IV NSCLC
Endpoints	**Primary** To assess whether the addition of radiotherapy to the remaining thoracic tumor burden following standard medical treatment results in a superior quality of life measured with lung cancer symptom scale (LCSS) in patients with stage IV non-small cell lung cancer. The measurements will be assessed at three months after randomization. **Secondary** Overall survival, progression-free survival, toxicity, longitudinal quality of life measurements
Design	Multicentre, randomized phase III trial. Patients will be registered for the study up-front but randomization will be performed after evaluation of response after three months of medical treatment. Randomization to thoracic radiotherapy or follow-up.

Population
 	
Inclusion criteria
	Patients with histologically verified NSCLC stage IV amenable to standard chemotherapy.
	
	• Histological or cytological confirmed non-small cell lung cancer (NSCLC)
	• Mixed histology allowed if all components are consistent with NSCLC.
	• Stage IV disease
	  o Previously untreated disease (before first line chemotherapy)
	  o No symptomatic brain metastases
	• Performance status (WHO) 0-2
	• FEV1 ≥ 1 L or >40% of predicted Written informed consent
	• Life expectancy ≥ 12 weeks
	• Platelet count ≥ 100,00/mm^3
	• Hemoglobin ≥ 10 g/dL

Exclusion criteria	• WBC ≥ 3,000/mm^3 • Kidney function allowing chemotherapy • Patients scheduled for standard platinum based chemotherapy, chemo-immunotherapy or immunotherapy in first line • Willing and able to comply with study treatment • Requirement for daily supplemental oxygen • Second primary malignancy within 3 years, except for any of the following which can be included even if diagnosed within the past 3 years: o Carcinoma in situ of the cervix o Non-melanoma skin cancer o History of low-grade (Gleason score ≤ 6) localized prostate cancer o Definitely treated Stage I breast cancer. o Other malignancy that was diagnosed and definitely treated ≥ 3 years ago with no subsequent evidence of recurrence • Concurrent severe and/or uncontrolled medical condition, including any of the following: o Angina pectoris o Congestive heart failure within the past 3 months, unless LVEF > 40% o Myocardial infarction within the past 6 months • Clinically significant infection • Psychiatric illness or social situation that would limit compliance with study requirements • EGFR mutation or ALK transformation detected
Treatment (s)	4 courses of platinum-based chemotherapy according to local tradition or 4 courses of chemo-immunotherapy or three months treatment of single immunotherapy. If stable disease (SD) or response (CR/PR) to initial therapy the patient will be randomized to standard follow-up or radiotherapy 3 Gy to a total dose of 36 Gy to primary tumor. Palliative radiotherapy for distant metastases outside thorax is allowed whenever needed. If need for symptom palliation, all

	patients could have radiotherapy even to the thorax. Maintenance chemotherapy or immunotherapy is allowed according to local practice, but should then be decided before randomization for both study groups. Bevacizumab maintenance is not allowed. Second line chemotherapy or immunotherapy is allowed when indicated.
Statistical analyses and sample size determination	The primary endpoint in the present trial is health-related QoL as measured with the LCSS, at three months. The sample size was calculated on the hypothesis that a scale score difference of >10 in the total LCSS scale (range 0-100) constitutes a clinically relevant group difference. With a power of 80% to detect this group difference as significant (p=0.05, two-sided test), with an assumed standard deviation of 22 and a loss of follow up of 20%, at least 162 randomized patients in total were required, 81 per group.
Timelines	• **Study duration per subject** • **Enrolment duration** First patient In : Feb 2017 Last patient In : Feb 2022 Last patient Out : Feb 2024 Estimated enrolment duration: 4 years

2 LIST OF ABBREVIATIONS

AE	Adverse event
ALAT	Alanine aminotransferase
ALK	Anaplastic Lymphoma Kinas
ALP	Alkaline phosphatase
ANC	Absolute neutrophil count
CR	Complete response
CRF	Case report form
CT	Computerized tomography
CTC	Common toxicity criteria
EC	Ethics committee
EGFR	Epidermal growth factor receptor
GCP	Good clinical practice
Hb	Haemoglobin
HrQoL	Health related Quality of Life
MC	Monitoring committee
RCC	Regionalt Cancer Centrum
RC	Review Committee
SAE	Serious adverse event
SD	Stable disease
SRC	Scientific and Review Committee
WBC	White blood cells
WHO	World Health Organisation

3 STUDY RATIONALE

3.1 Disease background and standard treament

Approximately 3.500 new cases of lung cancer are diagnosed in Sweden each year. Eighty percent have non-small-cell lung cancer NSCLC while the remaining has other histology, mainly small cell lung cancer. In the NSCLC population, approximately 50 % are diagnosed in stage IV, metastatic disease, and of them 70 % are in WHO performance status 0-2, adding up to 980 patients per year, which is the target population for this study. All these data are published from the Swedish National Lung Cancer Registry.

The standard treatment for this group of patients has been chemotherapy with a platinum doublet in four to six courses (cis- or carboplatin combined with either of vinorelbine, gemcitabine, paclitaxel, docetaxel or pemetrexed). Concomitant bevacizumab is sometimes used. For a proportion of patients with a good performance status and response to therapy, could maintenance therapy with pemetrexed or erlotinib or bevacizumab be an option. Radiotherapy is mainly used for symptom palliation, either to the primary tumor (dyspnea, cough, hemoptysis, vena cava superior syndrome etc.) or for treatment of distant metastases. In 2019 is treatment with a combination of a platinum doublet chemotherapy and immunotherapy with the PD-1 blocker pembrolizumab introduced for patients with a good performance status (WHO 0-1). Studies have shown survival advantages for this combination compared to chemotherapy alone (Gandhi et al 2018). For patients with tumors expressing high values of PD-L1 (> 50 %) immunotherapy with pembrolizumab alone showed better survival than chemotherapy (Reck et al 2019). This treatment is also now recommended in first line, according to the Swedish national guidelines.

There are some clinical data supporting radiotherapy upfront to the primary lung tumor to patients in stage IV and advanced non-curable stage III patients, where a prolongation of survival and improvement in quality of life have been observed. Two retrospective series in stage IV patients are published with 93 and 78 patients respectively, with 3 years overall survival of 25 and 13 % (Su et al 2014, Lopez Guerra et al 2012).

The Norwegian Lung Cancer Study Group has performed a randomized phase III trial for stage III patients not eligible for curative chemo-radiotherapy. 191 patients were randomized between four courses of chemotherapy (carboplatin and vinorelbine) or the same chemotherapy combined with radiation to 42 Gy in 15 fractions to the primary tumor and involved nodes. Overall survival was the primary endpoint and health-related quality of life and toxicity were secondary endpoints. The results showed a significant better overall survival for patients also receiving radiotherapy, median survival 12.6 and 9.7 months respectively ($p<0.01$), and a better quality of life but some more hospital admission due to toxicity. (Strøm et al 2013).

References:

Gandhi L, Rodríguez- Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, et al. Pembrolizumab plus chemotherapy in metastatic non–small-cell lung cancer. N Engl J Med. 2018;378(22):2078-92.

Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, et al. Updated analysis of KEYNOTE-024:pembrolizumab versus platinum-based chemotherapy for advanced non-small-cell lung cancer with PD-L1 tumor proportion score of 50% or greater. J Clin Oncol. 2019;37(7):537-46.

Su S, Hu Y, Ouyang W, Ma Z, Lu B, Li Q, LI H, Wang Z, Wang Y. The survival outcomes and prognosis of stage IV non-small-cell lung cancer treated with thoracic three-dimensional radiotherapy combined with chemotherapy. Radiotherapy and Oncology 290, 2014.

Lopez Guerra J, Gomez D, Zhuang Y, Hong D, Heymach J, swisher S, Lin S, Komaki R, Cox J, Liao Z. Prognostic impact of radiation therapy to the primary tumor in patients with non-small cell lung cancer and oligometastases at diagnosis. Int J Radiat Biol Phys 84, e61-67, 2012.

Strøm H, Bremnes R, Sundstrøm S, Helbekkmo N, Fløtten Ø, Assebø U. Current palliative chemoradiation leads to survival and quality of life benefits in poor prognosis stage III non-small-cell lung cancer: a randomized trial by the Norwegian Lung Cancer Study Group. British Journal of Cancer 109, 1467-1475, 2013.

3.2 Abscopal effect

There is a growing body of evidence for the phenomenon called abscopal effect. This is described as an immunologic response to localized radiation in areas outside the radiation field. This is initiated by cascades of complex downstream biological responses in tissue far away from the irradiated area. Release of tumor antigens is thought to stimulate the immune system (Reynders et al 2015, Siva et al 2013). This has also been shown in animal studies of Lewis lung carcinoma in mice, where local radiotherapy is essential for the effect (Camphausen et al 2003). It seems that addition of immunotherapy could even enhance this abscopal response, which has been shown for lung cancer patients with ipilimumab for example (Golden et al 2013).

References:

Reynders K, Illidge T, Siva S, Chang JY, de Ruysscher D. The abscopal effect of local radiotherapy: using immunotherapy to make a rare event clinically relevant. Cancer treatment reviews 41, 503-510, 2015.

Siva S, Mac Manus M, Martin R, Martin O. Abscopal effects of radiation therapy: a clinical review for the radiobiologist. Cancer letters 356, 82-90, 2015.

Campenhausen K, Moses M, Ménard C, Sproull M, Beecken WD, Folkman J, O´Reilly S. Radiation abscopal antitumor effect is mediated through p53. Cancer research 63, 1990-1993, 2003.

Golden E, Demaria S, Schiff P, Chachoua A, Formenti S. An abscopal response to radiation and ipilimumab in a patient with metastatic non-small cell lung cancer. Cancer Immunol Res 365-372, 2013.

3.3 Hypothesis

The hypothesis for this study is that addition of radiotherapy to the primary tumor and mediastinal nodes to medical treatment could reduce the tumor burden, partly as an abscopal effect, and thereby improving quality of life and possible also prolonging survival.

4 STUDY OBJECTIVES

4.1 Objectives

4.1.1 Primary Objectives

To assess whether the addition of radiotherapy to the remaining thoracic tumor burden following standard medical treatment results in a superior quality of life measured with lung cancer symptom scale (LCSS) in patients with stage IV non-small cell lung cancer. The comparison will be made at three months after randomization.

4.2.1 Secondary Objectives

Overall survival, progression-free survival, toxicity and longitudinal quality of life measurements.

5 DESIGN

Multicentre, randomized, phase III trial. Patients will be registered for the study up-front but randomization will be performed after evaluation of response, three months after initiating medical treatment with chemotherapy/ chemo-immunotherapy or immunotherapy. Randomization will be to thoracic radiotherapy or follow-up (1:1).

6 SELECTION OF PATIENTS

6.1 Inclusion criteria for registration

- Histological or cytological confirmed non-small cell lung cancer (NSCLC)
- Mixed histology allowed if all components are consistent with NSCLC.
- Stage IV disease
    - Previously untreated disease (before first line treatment)
    - No symptomatic brain metastases
- Performance status (WHO) 0-2
- FEV1 ≥ 1 L or >40% of predicted
- Written informed consent
- Life expectancy ≥ 12 weeks
- Platelet count ≥ 100,00/mm^3
- Hemoglobin ≥ 10 g/dl
- WBC ≥ 3,000/mm^3
- Kidney function allowing chemotherapy
- Patients scheduled for standard platinum based chemotherapy, chemo-immunotherapy or immunotherapy
- Willing and able to comply with study treatment

6.2

Exclusion criteria

- Requirement for daily supplemental oxygen
- Second primary malignancy within 3 years, except for any of the following which can be included even if diagnosed within the past 3 years:
    - Carcinoma in situ of the cervix
    - Nonmelanoma skin cancer
    - History of low-grade (Gleason score ≤ 6) localized prostate cancer
    - Definitely treated Stage I breast cancer.
    - Other malignancy that was diagnosed and definitely treated ≥ 3 years ago with no subsequent evidence of recurrence
- Concurrent severe and/or uncontrolled medical condition, including any of the following:
    - Angina pectoris
    - Congestive heart failure within the past 3 months, unless LVEF > 40%
    - Myocardial infarction within the past 6 months
- Clinically significant infection
- Psychiatric illness or social situation that would limit compliance with study requirements
- EGFR mutation or ALK-EML4 rearrangement detected

7 FLOW CHART

	SCREENING/ BASELINE	Reassessment	Randomization	ASSESSMENT AFTER Randomization	POST START OF STUDY TREATMENT (PSOST) FOLLOW-UP					
CLINICAL VISIT	1			Follow-up 1	2	3	4	5	6	
MONTH	X			3	6	9	12	18	24	EOS
Written informed consent	X									
Inclusion/exclusion criteria	X		x							
Computerized Tomography, CT[1]	X	x		X	X	X	X	X	X	
PET[1]	(X, optional)									
QoL	X	x		X	x	X	x	X	x	
Medical history	x	x								
Physical examination	X	x		X	X	X	X	X	X	
Body weight	X	X		X	X	X	X	X	X	
Pre-treatment weight loss	X									
Height	X									
Performance status according to WHO	X	x		X	X	X	X	X	X	
Haematology[5]	x	x		x	x	x	x	x	x	
Biochemistry[5]	x	x		x	x	x	x	x	x	
Biological sampling[4]	x	x		X						
Assessment of symptoms/Adverse events (NCI-CTC) Version 4.03 [3]	X			X	X	X	X	x	X	x
Spirometry[6]	X		X[7]							

1. Should not be more than 6 weeks before inclusion
2. Recommended but not mandatory
3. Serious Adverse Events should be reported within 24h. SAE have to be declared up to 30 days after last study drug infusions
4. Optional, see 8.5
5. Within 72 hours
6. Should be done within 8 weeks
7. If spirometry is done without CO-diffusion measurements, a new spirometry should be done for patients randomized to radiotherapy including this test

8 VISIT SCHEDULE AND TREATMENT ASSESSMENTS

8.1 Pre study Assessment

Screening < 7 days before start of chemotherapy

- TNM classification (7th edition)
- Histologically or cytologically confirmed diagnosis
- Localization of metastases
- Medical history
- Physical examination
- Performance status according to WHO
- Assessment of quality of life according to LCSS
- Pre-treatment weight loss (In the 6 months prior to study enrollment)
- Body Weight and height
- Assessment of symptoms at baseline according to NCI-CTC criteria version 4.03.

The following assessments must be performed:

- CT of thorax and upper abdomen (allowed up to 6 weeks).
- Spirometry and DLCO (allowed up to 8 weeks). If DLCO is not included in the spirometry, an additional spirometry must be performed for patients randomized to radiotherapy including that.
- Haematology ***(****Haemoglobin, Hb****,*** *White Blood Cell Count, WBCC****,*** *Total Platelet Count, TPK****,*** *Absolute Neutrophil Count, ANC)* within 72 hours.

  Biochemistry *(Serum creatinine, Serum calcium and albumin, Bilirubin, Alkaline Phosphatase, Aspartate transaminase - SGOT (ASAT), Alanine transaminase - SGPT (ALAT), Lactate Dehydrogenase – LD, Sodium, Potassium, Magnesium)* Within 72 hours.

- Biological sampling- Optional *(Plasma and whole blood sampling for Exploratory Objectives)*
- PET-CT –Optional

8.2 Response evaluation after chemotherapy should be performed day 8-21 in the fourth chemotherapy cycle.

8.2.1 Reassessment

- CT thorax and upper abdomen.
- Evaluation of known metastatic sites with appropriate method
- Hematology

- Biochemistry
- Performance status WHO
- Quality of life assessment LCSS
- Physical examination and weight
- Biological sampling -Optional *(Plasma and whole blood sampling for Exploratory Objectives)*

8.3 Randomization

If the reassessment shows SD, PR or CR according to RESIST criteria (see 18.3) patients should be randomized 1:1 to receive thoracic radiotherapy or not. Randomization should be done within 7 days from evaluation of tumor response. Decision on maintenance with chemotherapy or immunotherapy or not should be taken before randomization. Randomization is done by telephone to RCC Väst 010-4412823, phone is open 8-16.

8.3.1 Follow-up 1, 3 months after randomization

- Physical examination
- Recording of persistent or new toxicity
- Performance status (WHO)
- CT
- Weight
- Haematology and biochemistry sampling
- Quality of life assessment LCSS
- Biological sampling –Optional *(Plasma and whole blood sampling for Exploratory Objectives)*

8.3.2 Follow-up 2-6

6, 9, 12, 18 and 24 months after start of study therapy

- Physical examination
- Recording of persistent or new toxicity
- Performance status (WHO)
- Weight
- Haematology and biochemistry
- Quality of life assessment LCSS.
- CT

8.4 Quality of life

Quality of life assessment
The Lung Cancer Symptom Scale (LCSS) is a site-specific quality-of-life (QoL) measure focusing on physical and functional dimensions of health-related QoL. It consists of nine visual analogue scales (0-100 mm) assessing QoL in the past 24 hours, including symptom measures (i.e. appetite, fatigue, cough, dyspnea, hemoptysis, and pain), effects on activities of daily living, and overall QoL (12). A summary score of all nine scales could be calculated (range 0-100, lower scores representing less symptoms) and used as outcome measure.

Content validity of the LCSS has been confirmed by expert and patient surveys, indicating a 96% agreement for all items among experts (24 medical oncologists), and a good matching with own experience in patients (121 patients with advanced lung cancer) (1). Reliability has been documented with an internal consistency of >0.8 in the total score, a good test-retest reliability (r>0.75), and a high inter-rater agreement (95-100%) among experts (2). Construct and criterion validity (i.e. comparison and correlations with gold standard measures) has been proven (1).

The LCSS has been extensively used in trials of lung cancer (3).

The LCSS will be administered at baseline, 3, 6, 9, 12, 18 and 24 months after randomization.

1. Hollen PJ, Gralla RJ, Kris MG, Potanovich LM. Quality of life assessment in individuals with lung cancer: Testing the lung cancer symptom scale (LCSS) Eur J Cancer. 1993;29A Suppl 1:S51–S58.
2. Hollen PJ, Gralla RJ, Kris MG, Cox C, Belani CP, Grunberg SM, et al. Measurement of quality of life in patients with lung cancer in multicenter trials of new therapies. psychometric assessment of the lung cancer symptom scale. Cancer. 1994 Apr 15;73(8):2087–2098.

3. LCSS bibliography. www.lcss-ql.com/bibliography.htm

8.5 Exploratory Objectives

For subjects who provide a separate informed consent, blood-sampling for exploratory biomarker analyses will be collected at visits 1, 2 and 4. The sampling and storage procedure are defined in a separate protocol (*Biological sampling*). Investigations will be carried out in blood samples in order to explore candidate predictive and prognostic biomarkers in blood. A customized panel of tumour and tumour stroma related proteins will be assessed using the Luminex platform (Luminex corp, Austin TX) for multiplex targeted analysis of changes in the proteome. Based on these findings further analysis of metabolic changes downstream the proteome will be conducted using unbiased mass-spectrometic metabolomic profiling. Changes in the proteomic and metabolomics fingerprints will be analysed using multivariate methods. The main objective of the exploratory part of the study is to find clinically useful predictive and prognostic biomarkers for lung cancer treatment.

9.0 RADIOTHERAPY

9.1 Patient pre-treatment preparation

The patient shall be positioned with the arms above the head in supine position. Immobilization devices, such as vacuum bags, Wing Step are used according to local routines. For patients randomized to radiotherapy, the spirometry must contain a CO-diffusion test. If that is done at inclusion in the study, it must be completed.

The patient reference coordinate system is defined by using tattoos or ink marks

9.2 Pre-treatment imaging

For structure delineation CT imaging shall be performed with ≤ 5 mm slice thickness. The use of i.v. contrast is optional.

The CT scanning shall be performed from larynx to 5 cm below the diaphragm.

9.3 Specification of radiation treatment

Volume specification

The different volumes of interest shall be defined in agreement with ICRU Report 83

Gross Tumour Volume (GTV):
The GTV includes the primary lung tumour and pathological lymph nodes defined from post-chemotherapy CT, pre-treatment PET-CT (if performed - optional) and pre-treatment bronchoscopy. Atelectasis, if present, shall be included in the GTV if it is not possible to separate from the primary tumour

Clinical Target Volume (CTV)
The CTV includes GTV + local subclinical extension. Approximately 1 cm margin shall be added to the GTV, with proper adjustment to big vessels, heart, esophagus, vertebrae etc. If a mediastinal pathological lymph node is located with a distance from the primary tumor, resulting in two separate target volumes, the unaffected node level in between should be included in the CTV. Apart from that, no adjuvant volumes shall be included. If CR is achieved after chemotherapy, CTV will include the area of former primary tumor and previously affected nodal stations without margin

Planning Target Volume (PTV)

Appropriate margins shall be added to the CTV to take into account the effects of organ and patient motions and inaccuracies in beam and patient setup in order to ensure that the prescribed dose is actually absorbed in the CTV according to local routines

Organs at risk
Organs at risk are the heart, lungs, spinal cord and the esophagus and shall be delineated as follows.
OAR: Heart, lungs and esophagus are outlined without margins.
PRV$_{\text{spinal cord}}$ is outlined with limit to bone and the volume then includes a margin to the spinal cord.

Absorbed dose prescription
The prescribed total dose is 36 Gy, specified as dose to CTV.
For treatment planning optimization physical objectives and constraints shall be prioritized according to priority list

Priority list

Priority	Volume	Constraints
1	PRV spinal cord	D_{max} 36 Gy (100%)
2	CTV	> 95 %
3	PTV	>90%
4	OAR lungs (both lungs minus GTV)	V20 < 45%
5	OAR esophagus	Max dose <37,8 Gy (105%)
6	OAR heart	Not applicable

Fractionation and treatment time
Radiotherapy is given 5 days/week with 12 fractions of 3 Gy
Maximum treatment days is 20 days

Relation to other therapies
Radiotherapy is given after 4 cycles of standard chemotherapy to patients with proven SD/PR/CR.
Radiotherapy shall start within 2 weeks from randomization. No concomitant chemotherapy or immunotherapy should be given, i.e. five days before and after first and last fraction of radiotherapy.

Treatment planning and delivery
The radiation treatment shall be given with photon therapy. 3DCRT, IMRT or rotational technique (for example VMAT) should be used.

Potential radiation toxicity:

Lungs
Radiation-induced lung toxicity is defined as an early side- effect, pneumonitis (1-6 months after radiotherapy) and late fibrosis (> 6 months after radiotherapy). A reduction in lung function is initially usually reversible and later more persistent.

The estimated risk of lung injury is correlated to mean lung dose, irradiated lung volume, fractionation and normal tissue complication probability. An acceptable estimated risk of side-effects can be about 20-25 % risk of grade 2 pneumonitis. This risk estimation seems to correspond to a mean lung dose < 18-20 Gy, and V20 < 30 % (Kong, Hayman et al. 2006)). For patients with previous lung disease, the risk can be higher.

Esophagus
Esophagitis, an inflammatory reaction due to cell depletion in the mucosa is seen two to three weeks after start of radiotherapy. With the actual fractionation schedule this will be transient and mostly fade away after one or two weeks. Occasionally mild analgesics and softer nutrients are needed.

Spinal cord
The doses to the spinal cord are below the tolerance level for injury in this protocol.

Heart
There is no consensus for recommended maximum doses to the heart. The spinal cord and the lungs will often be the dose-limited organs. It is recommended to keep the irradiated volume of the heart as small as possible without compromising the target volume.

10 MEDICAL TREATMENT

10.1Chemoterapy

Chemotherapy is given before randomization with 4 courses of a platinum-based doublet in accordance with local practice. A minimum of three courses must be given before randomization. If maintenance chemotherapy is planned, the radiotherapy is preferably given in between cycles.

10.2Chemo-immunotherapy

Chemo-immunotherapy is given before randomization with 4 courses of a platinum-based doublet in combination with a PD-1 blocker in accordance with local practice. A minimum of three courses must be given before randomization. If maintenance immuno- or chemo-immunotherapy is planned, the radiotherapy is preferably given in between cycles.

10.3Immunotherapy

Patients scheduled for primary immunotherapy as single agent should receive three months of therapy (i.e. 5 courses normally, if a schedule with treatment every third week is used) before evaluation and randomization. If prolonged treatment is planned immunotherapy should not be given concomitant with radiotherapy.

11 DISCONTIUATION OF TREATMENT

- Patient refusal – patients are free to discontinue the study or treatment at any time by withdrawing their consent, without giving any reason.
- If the patient for any reason refuses further treatment, but does not withdraw consent, the patient will continue to be followed up according to the study schedule
- Progressive disease at any time during treatment is a valid reason for stopping the treatment
- Adverse reactions that are severe, life threatening or unacceptable, will preclude further treatment.

12 SAFETY ASSESSMENTS AND REPORTING

12.1 Follow-up assessment

All Adverse Events (AEs) or Serious Adverse Events (SAEs) are recorded in appropriate CFR form and reported using NCI-CTCAE v 4. http://ctep.cancer.gov/reporting/ctc.html

All SAEs are reported on specific SAE forms and sent to Klinisk Prövningsenhet, Department of Oncology, Sahlgrenska University Hospital, Göteborg
fax number: 031-823931 (telephone number: 031-3427654) within 24 hours, or as soon as it comes to the investigators knowledge. The investigator at the respective site is responsible for this being done according to GCP rules.

12.2 Recording of adverse events (AE)

All AEs must be documented in the appropriate section of the CRFs. For SAEs, a SAE report form (initial or follow-up) must be completed in addition.
The following aspects must be recorded for each event in the CRF:

- A description of the AE in medical terms, not as reported by the subject
- The date of onset (start date)
- The time of onset in case the event started on the day of cetuximab administration (start time)
- The date of recovery (stop date)

During clinical visits, the investigator must seek information on adverse events by specific questioning and, as appropriate, by physical examination. Information on all adverse events should be recorded immediately in the Adverse Event module of the CRFs using the CTCAE version 4.

All adverse events, present at entry to the study and occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization or until it has been determined that study treatment or participation is not the cause. Serious adverse events which are still ongoing at the end of the study period must be followed to determine the final outcome.
Any serious adverse event, which occurs after the study period and is considered to be possibly related to study treatment or study participation should be recorded and reported immediately.

The grade as assessed by the investigator according to the definitions in NCI CTC version 4 :

- Grade 1 = mild
- Grade 2 = moderate
- Grade 3 = severe
- Grade 4 = life-threatening or disabling
- Grade 5 = death related to AE

Not Related; There is no temporal relationship to the study treatment = radiotherapy, or there is a reasonable causal relationship between another drug, concurrent disease or circumstance and the AE.

Not Likely; There is a temporal relationship to the radiotherapy, but there is not a reasonable causal relationship between the study treatment and the AE,

Probable; There is a reasonable causal relationship between the study treatment and the AE.

Other action (none, concomitant medication given, new or prolonged hospitalization, procedural surgery

The outcome according to the following definitions:

- Recovered with sequelae
- Recovered without sequelae
- Ongoing, no therapy
- Ongoing, therapy
- Died
- Change in toxicity grade/severity
- Seriousness: yes or no

In case of SAEs it must be indicated whether the SAE is the leading event, i.e. the primary medical reason for SAE reporting.

A Serious Adverse Event (SAE) is an event which

- Results in death
- Is life-threatening
- Is disabling
- Requires hospitalization, whether initial or prolonged, and does not include planned hospitalization
- Requires intervention to prevent permanent impairment/damage

The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death had it been more severe.

Events not to be treated as SAEs

Progression of disease is not to be regarded as a SAE.

Due to the seriousness of the disease in this study, certain conditions defined as SAEs will be excluded from expedited reporting on a SAE report form:

- Elective hospitalization and surgery for treatment of disease
- Elective hospitalization to simplify treatment or study procedures

12.3 Patient withdrawal

- Any subject who experiences an adverse event may be withdrawn at any time from the study treatment at the discretion of the investigator
- If the adverse event is related to an overdose of study medication, the SPC should be consulted for details of any specific actions to be taken.
- If a subject is withdrawn wholly or in part because of an adverse event, this should be noted on the Study treatment form in addition to the Adverse Event section. The sponsor-investigator should be informed without delay of all subjects who are withdrawn for this reason.
- Any death occurring between the study inclusion and 30 days following the last infusion must be reported as a SAE within 24 hours, regardless of the relation to study medication. Death occurring during the study follow-up period (i.e. later than 30 days after the last infusion) need only to be reported as serious adverse event if it is thought that there is a possible relation to study drug(s) (possible, probable). All deaths should be reported on the death report form section on the CRF regardless of cause.

13 MANAGEMENT OF DATA

13.1 Case Report Form Handling

Case record forms (CRFs) will be provided to record all the study data. Data must be entered onto the case report forms completely and legibly. The investigator will ensure that all copies of the forms are readable and will also verify that all data contained on these forms are accurate. All the forms should be signed.

Any subsequent alterations to the data must be made by striking out the previous entry with a single line and by writing the new value next to it. All such changes must be initialled and dated.. Whiting or scribbling out the errors is not acceptable.

When the monitor reviews the CRFs, certain queries may arise. These will be documented in writing and the resolution will also be noted in writing.

13.2 Patient data collection and handling

Regionalt Cancer Centrum Väst (RCC) will be responsible for Data Management in the study. All data will be recorded in the Case Report Form. Monitoring of data must be performed by qualified designated personnel.

13.3 Site data quality control and monitoring and stopping rules

Monitoring
The study will be monitored according to ICH/GCP by site visits. During site visits, the monitor should review original patient records and document retention. Additionally, the monitor should observe study procedure and will discuss any problem with the investigator. The investigator will provide direct access to source data/documents for trial related monitoring, audits, Ethics Committee review and regulatory inspections.
Monitoring will be provided by Klinisk Prövningsenhet, Department of Oncology, Sahlgrenska University Hospital, Göteborg.

Stopping rules
Toxicity of radiotherapy will be evaluated and protocol modification considered if excessive toxicity is observed. Late toxicities will be evaluated by Quality of Life questionnaire.

The trial will stop prematurely for the following considerations:

- When emerging adverse events are of such a serious nature that continuation of the trial becomes unacceptable.
- When the recruitment is too low to expect completion of the study in its present form within an acceptable period of time (inclusion estimated to be 24 months).
- When the number of dropouts as described above (10.7) is too high and this situation is not acceptable for a period of time.

14 STATISTICAL CONSIDERATIONS

14.1 Statistical analysis plan

Sample size
The primary endpoint in the present trial is health-related QoL as measured with the LCSS, at three months. The sample size was calculated on the hypothesis that a scale score difference of >10 in the total LCSS scale (range 0-100) constitutes a clinically relevant group difference. With a power of 80% to detect this group difference as significant (p=0.05, two-sided test), with an assumed standard deviation of 22 and a loss of follow up of 20%, at least 162 randomized patients in total were required, 81 per group.

15 TASKS AND RESPONSIBILITIES

15.1 Responsibilities of the study committee

The Scientific and Review Committee (SRC) consisting of SLUSG, Swedish Lung cancer Study Group, will be responsible for scientific advice and recommendations on:

- Protocol and data collection form
- Assess efficacy and safety issues in this study
- Verify patient eligibility
- Methodology
- Data analysis plan
- Development of publication guidelines
- Secure Good Clinical Practice (GCP) to be followed

In a situation where other countries (regions) will enter the study, this committee will expand so that a balanced representation will be pursued. The committee will take decisions with a simple majority as the basic principle in case a consensus based decision can otherwise not be reached. The committee will ensure that all participants are encouraged to engage themselves in sub-studies as well as in translational research projects originating from the basic study population. If individual trial lists or centers are interested in specific sub-analyses or specific subgroup studies, the committee has to be addressed through a formal application and the committee will give approval with delineation of the details of the conduct of the study as well as the publication principles. In order to speed up the processing of similar applications the committee will be able to take decisions through mailing and/or telephone conferencing. Again simple majority principles will be applied. The committee will be competent to make decisions provided that half of the delegates are present or have given their written approval. If the written approval not is obtained, the opinion of the majority of the present members will be applied.

15.2 Participating Physicians

The investigator (according to applicable regulatory requirements), or a person designated by the Investigator, and under the Investigator's responsibility, should fully inform the subject of all pertinent aspects of the registry including the written information.
The Participating Physicians will perform the study in accordance with this protocol and will verify and check that the information reported in the CRF is as precise and accurate as possible.

It is the Participating Physician's responsibility to fill in the CRF, to record all data pertinent to the clinical investigation and obtain written informed consent from patients prior to inclusion in the study.

15.3 Responsibilities of the sponsor

The Sponsor of the study is responsible for taking all reasonable steps and providing adequate resources to ensure the proper conduct of the study as regards:

- local submission(s) complying with data protection rules
- any other local regulations
- validity of the data recorded (Quality control of the data collected will be performed on site on a predefined percentage of sites and patients).

15.4 Record retention and confidentiality

The Participating Physician shall arrange for the retention of the subject identification codes after the completion or discontinuation of the study. Also patients' files and other source data shall be kept for the maximum period of time permitted by the hospital, institution or private practice.
In addition the investigator will comply with specific local regulations/ recommendations with regards to patient record retention. Copies of all pertinent information, including patient identity and allocation number and individual patient data records, will be retained in a confidential manner by the investigator for a minimum period of 15 years from study completion.

The investigator is responsible for keeping a list of all patients (who have received study treatment) including patient numbers, full names and last known addresses. The patients should be informed in writing that the results will be stored and analysed in a computer, that national data laws will be followed and subject confidentiality will be maintained.

The patients should also be informed in writing about the possibility of audits by authorised representatives of the regulatory authorities, in which case a review of those parts of the hospital records relevant to the study may be required, with due consideration for patient integrity.

15.5 Data Protection

The patient's personal data and Investigator's personal data which may be included in the Sponsor database shall be treated in compliance with all local applicable laws and regulations. When archiving or processing personal data pertaining to the Investigator and/or to the patients, the Sponsor shall take appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

16 ETHICAL AND ADMINISTRATIVE CONSIDERATIONS

This study will be conducted in accordance with the protocol and the ethical principles put forward in the Declaration of Helsinki (52nd WMA General Assembly, Edinburgh, Scotland, October 2000) and in accordance with GCP (CPMP/ICH/135/92) rules.

The subject's personal data and Investigator's personal data which may be included in the Sponsor database shall be treated in compliance with all local applicable laws and regulations.
The rights, safety and well being of the trial subjects are the most important considerations and should prevail over interests of science and society.
Study personnel involved in conducting this trial will be qualified by education, training and experience to perform their respective tasks.
This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC), in agreement with local rules, for formal approval.

16.1 Informed Consent

The subject should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prio to a subject's participation in the study, the written Informed Consent Form should be signed, name filled in and personally dated by the subject and by the person who conducted the informed consent discussion. A copy of the signed and dated written Informed Consent Form will be provided to the subject.

17 REPORTING AND PUBLICATIONS

A study report will be prepared after the end of the study. The study will be published once it is completed and the final analysis has been performed. Any publication based on the data from this study proceeds from the investigator group, with specification of the participating clinics and

responsible contacts. The names on the author list will be given according to the active participation in the design of the protocol, in the recruitment of eligible and evaluable patients, in the compilation of results and in the production of the article. Investigators recruiting >10% of patients will be cosidered as authors. All participating clinics with responsible investigator will be named in a special appendix.

18 APPENDIX

18.1 WHO Performance Status

Activity Status	Description
0	Asymptomatic, fully active, and able to carry on all predisease performance without restrictions.
1	Symptomatic, fully ambulatory but restricted in physically strenuous activity and able to carry out performance of a light or sedentary nature, eg, light housework, office work.
2	Symptomatic, ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours: in bed less than 50% of day.
3	Symptomatic, capable of only limited self-care, confined to bed or chair more than 50% of waking hours, but not bedridden.
4	Completely disabled. Cannot carry on any self-care. Totally bedridden.
5	Dead

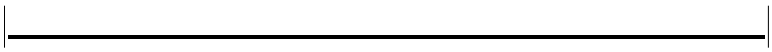
18.2 Lung Cancer Symptom Scale

LUNG CANCER SYMPTOM SCALE (LCSS): Patient scale (Swedish version)

Anvisningar: Var snäll och markera utefter varje linje där symtomen av din lungcancer UNDER SENASTE DAGEN (inom sista 24 timmarna) beskrivs bäst.

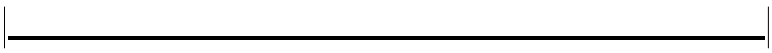
1. Hur är din aptit?

   Så bra den kan vara — Så dålig den kan vara



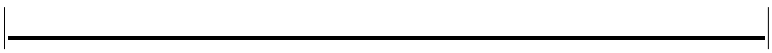
2. Hur mycket trötthet känner du?

   Ingen — Så mycket som det är möjligt att känna



3. Hur mycket hosta har du?

   Ingen — Så mycket den kan vara



4. Hur mycket andfåddhet känner du av?

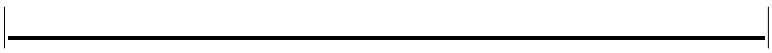
   Ingen — Så mycket som det är möjligt att känna

5. Hur mycket blod ser du i ditt slem?

   Inget — Så mycket det kan vara

6. Hur mycket smärta känner du?

   Ingen — Så mycket som det är möjligt att känna



7. Hur svåra är dina symtom av lungcancer?

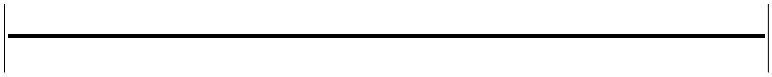
   Jag har inga — Så svåra de kan vara

8. Hur mycket har din sjukdom påverkat din förmåga att utföra normala aktiviteter?

   Inte alls — Så mycket att jag inte kan göra något för mig själv

9. Hur skulle du bedöma din livskvalitet idag?

   Mycket hög — Mycket låg



18.3 Recist criteria 1.0

Complete response (CR): Disappearance of all clinical evidence of tumor (target and non-target lesions), determined by two observations not less than four weeks apart.

Partial response (PR): 30% or greater decrease in the sum of the longest diameter of target lesions, determined by two observations not less than 4 weeks apart. No unequivocal increase in the size of non-target lesions or the appearance of new lesions may occur.

Stable disease (SD): Steady state of response (i.e. not PR and not PD) of at least 9 weeks duration. There may be no appearance of new lesions for this category.

Progressive disease (PD): 20% or greater increase in the sum of the longest diameter of target lesions or unequivocal progression of non-target lesions. Appearance of new lesions will also constitute progressive disease.

Biological sampling

18.4 PROCEDUR FÖR PROVOMÄNDERTAGANDE MARS

Syftet med ovan rubricerade studie är att hitta radiologiska och biologiska markörer på respons tidigt under strålbehandlingen. Under studien tas blodprover enligt studiemallen. Nedan beskrivs proceduren för omhändertagande av blodprover inom ramen för studien.

Studieprover

Studieprover tas för att möjliggöra senare analyser av biomarkörer. Provtagningen samordnas med de tillfällen patienten skall genomgå procedur för blodprover, dvs vid baseline, vid randomisering samt tre månader efter randomisering.
Studieprover tas i två typer av rör:

1. **Lila 5 mL L provrör (Vacutainer): EDTA** för tillvaratagande av plasma som fryses i aliqouter i -70°C.
2. **Grönt 5 mL provrör (Vacutainer). Heparin.** för tillvaratagande av plasma som fryses i aliqouter i -70°C

Provtagningsprocedur för studieprover:
Instruktioner för provtagare

1. Proverna tas efter **5 minuters vila**.
2. Identitetskontroll sker innan provtagning
   - Utför identitetskontroll genom att be patienten själv uppge personnummer och namn.
3. **Tag fram två venojectrör. Ett EDTA** (lila kork) och **ett Heparin** (grön kork) Märk rören med personnummer och studie ID. Etiketter från BBN
4. Använd gärna grov kanyl i syfte att undvika hemolys, om möjligt
5. Patienten bör om möjligt ej knyta handen vid provtagningen. Tag **5 ml blod** (utan stas om möjligt) i EDTA-röret (lila kork) samt 5 mL blod i heparinröret (grön kork). Vid behov av stas ta gärna studieproverna sist.
6. Skicka provrören omedelbart till biobank eller motsvarande. Provet bör vara biobanken tillhanda inom ca 15 minuter. Bifoga följesedel med namn, personnummer och studie ID.

Instruktioner för provhantering vid biobank eller motsvarande

7. Kontrollera provrörens ID märkning mot följesedel vid utplock från rörpost
8. Ställ rören i provrörsstället och låt stå i 15 minuter
9. Ta fram **16 st frysrör med 2D kod**. Märk rören med studie ID samt datum, samt B för baseline, R för randomisering och 3M för tre månaders kontroll. Och **2 st engångspipetter**
10. Centrifugera proverna i **15 min med 3200 varv** (1500G).
11. Använd engångspipett. Pipettera upp **8 st 0,25 ml plasmaprov ur EDTA-röre**t (lila kork).
12. Använd den andra engångspipetten och **upprepa proceduren** med det heparin-behandlade blodprovet (grön kork). 8 st plasmaprov à 0,25 ml vardera i frysrören.
13. Kontrollera att locken är förslutna väl (skruva igen ordentligt!) och placera rören i nästa lediga rad i infrysningskartongen som finns i frysen och återställ därefter kartongen till frysförvaring.
14. Proverna skall vara i frysen **(-80^0) inom 1 timme.**