NTNU Norwegian University of Science and Technology

ST. OLAVS HOSPITAL TRONDHEIM UNIVERSITY HOSPITAL

Randomized phase III trial investigating the survival benefit of adding thoracic radiotherapy to durvalumab (MEDI4736) immunotherapy plus chemotherapy in extensive stage small-cell lung cancer

Clinical study protocol

EudraCT no: 2021-001648-91

Sponsor

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Signature page

I hereby declare that I will conduct the study in compliance with the protocol, ICH GCP and applicable regulatory requirements.

Name	Title	Role	Signature	Date
Magnus Steigedal	Head of Department	Sponsor Representative		
Bjørn H. Grønberg	Professor and Consultant	Chief Investigator		

1. PROTOCOL SYNOPSIS

Study title: Randomized phase III trial investigating the survival benefit of adding thoracic radiotherapy (TRT) to durvalumab immunotherapy plus chemotherapy in extensive stage small-cell lung cancer
Protocol version number: 1.0
Clinical phase: Randomized phase III
Study duration: From 2021 until 2028
Investigational therapies and reference therapy: • Reference therapy: Durvalumab plus carboplatin/etoposide • Investigational therapy: Durvalumab plus carboplatin/etoposide and TRT
Research hypotheses: The main hypothesis is that adding TRT to durvalumab plus chemotherapy provides a survival benefit for patients with extensive stage (ES) small-cell lung cancer (SCLC). Specifically, we hypothesize that: • combining TRT, durvalumab and chemotherapy is feasible and well tolerated • adding TRT improves survival, response rates, and PFS • the patients who benefit the most from the study treatment can be identified through analyses of tissue, blood and stool samples • toxicity of prophylactic cranial irradiation (PCI) is acceptable in ES SCLC patients who receive durvalumab plus chemotherapy
Objectives: *Primary Objective:* To investigate whether adding TRT to durvalumab plus chemotherapy improves 1-year survival. *Secondary Objectives:* To investigate whether adding TRT improves 2-, 3-, 4- and 5-year overall survival. To investigate whether adding TRT improves overall response rates, response rates in non-irradiated lesions and PFS. To investigate whether TRT improves local control. To compare the frequency and severity of adverse events between the treatment arms. To compare health related quality of life between treatment arms. *Exploratory Objectives:* To compare the duration of severe adverse events between the treatment arms. To compare the frequency and timing of brain metastases between treatment arms. To assess cognitive function in the whole study cohort and compare cognitive function between those who receive PCI and those who do not. To investigate associations between outcomes of study treatment and biomarkers in tissue, blood and stool (e.g. ctDNA in blood, miRNA, gut microbiome).

Endpoints:

Primary Endpoint:

1-year overall survival

Secondary Endpoints:

2-year, 3-year, 4-year and 5-year overall survival

Overall response rates

Response rates in non-irradiated lesions

Progression free survival

Progression free survival in non-irradiated lesions

Local control rates in the thorax

Frequency and severity of adverse events

Health-related quality of life

Exploratory Endpoints:

Duration of severe adverse events

Frequency and timing of brain metastases

Cognitive function in patients who receive PCI and those who do not

Associations between outcomes of study treatment and biomarkers in tissue, blood and stool (e.g. ctDNA in blood, miRNA and gut microbiome).

Study population:

Patients with ES SCLC eligible for chemo-immunotherapy and TRT.

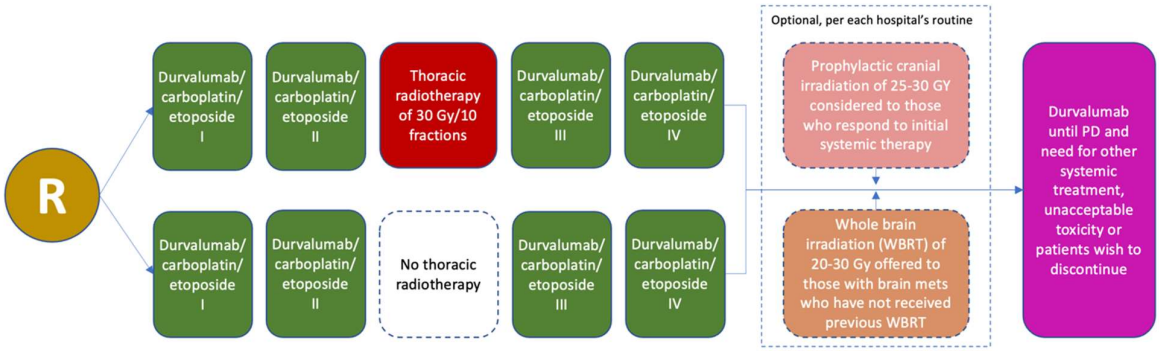
Number of centers: Approx. 25

Number of patients: Approx. 302

Study design:

Open label randomized phase III trial

Figure 1 Study design



Randomization:

Patients will be randomized 1:1 in blocks of various sizes to receive chemo-immunotherapy alone or chemo-immunotherapy plus TRT stratifying for presence of liver metastases (yes vs. no) and presence of brain metastases (yes vs. no).

Inclusion criteria:

1. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. Written informed consent

and any locally required authorization (e.g. Health Insurance Portability and Accountability Act in the US, European Union [EU] Data Privacy Directive in the EU) obtained from the patient/legal representative prior to performing any protocol-related procedures, including screening evaluations.

2. Age ≥ 18 years at time of study entry.
3. ECOG performance status of 0 or 1.
4. Body weight >30 kg.
5. Adequate normal organ and marrow function as defined below:
   - Haemoglobin ≥10.0 g/dL.
   - Absolute neutrophil count (ANC) ≥1.5 × 10^9 /L
   - Platelet count ≥100 × 10^9/L
   - Serum bilirubin ≤1.5 x institutional upper limit of normal (ULN). This does not apply to patients with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of hemolysis or hepatic pathology).
   - ALT (SGPT) ≤2.5 x institutional upper limit of normal unless liver metastases are present, in which case it must be ≤5 x ULN.
   - Measured creatinine clearance (CL) >40 mL/min or Calculated creatinine CL>40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance.
6. Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow-up.
7. Life expectancy of at least 3 months.
8. At least 1 lesion in the thorax, not previously irradiated, that qualifies as a RECIST 1.1 target lesion (TL) at baseline and is possible to irradiate to 30 Gy in 10 fractions. Tumor assessment by computed tomography (CT) scan or magnetic resonance imaging (MRI) must be performed within 28 days prior to randomization.
9. Histologically or cytologically confirmed SCLC. Mixed histology may be acceptable as long as the SCLC component accounts for more than 90%.
10. Stage IV disease according to the TNM v8. Patients with stage III disease are eligible if the disease is too widespread to be treated as limited stage SCLC.
11. Pulmonary function: FEV1 >1 L or >30 % of predicted value and DLCO >30 % of predicted value.
12. Female patients of childbearing potential (postmenarcheal, not postmenopausal [>12 continuous months of amenorrhea with no identified cause other than menopause], and no surgical sterilization) should use highly effective contraception and take active measures to avoid pregnancy while undergoing systemic study therapy and for at least 5 months after the last dose.
13. Patients with brain metastases are eligible provided they are asymptomatic or treated and stable on steroids and/or anticonvulsants prior to the start of treatment.

Exclusion criteria:

1. Participation in another clinical study with an investigational product during the last 30 days.
2. Concurrent enrolment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study.
3. Previous chemo- or radiotherapy for SCLC. Patients who have undergone surgery, but no adjuvant therapy are eligible.
4. Any unresolved toxicity NCI CTCAE Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria.
5. Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the Chief Investigator.

6. Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab may be included only after consultation with the Chief Investigator.
7. Any concurrent chemotherapy, investigational product or biologic cancer therapy.
8. Any prior checkpoint inhibitor therapy, including durvalumab.
9. Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of study drugs.
10. Immediate need for thoracic radiotherapy or bulky disease outside the thorax, or need for such radiotherapy before completion of chemo-immunotherapy
11. Major surgical procedure within 28 days prior to the first dose of study drugs. Note: Local surgery of isolated lesions for palliative intent is acceptable.
12. History of allogenic organ transplantation.
13. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). The following are exceptions to this criterion:
    a. Patients with vitiligo or alopecia.
    b. Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement.
    c. Any chronic skin condition that does not require systemic therapy.
    d. Patients without active disease in the last 5 years may be included but only after consultation with the Chief Investigator.
    e. Patients with celiac disease controlled by diet alone.
14. Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia or QTcF value >470 ms on ECG, interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent.
15. History of another primary malignancy except for:
    a. Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of IP and of low potential risk for recurrence.
    b. Localized breast or prostate cancer treated with hormonal therapy alone.
    c. Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
    d. Adequately treated carcinoma in situ without evidence of disease.
16. Leptomeningeal carcinomatosis.
17. Untreated, symptomatic central nervous system (CNS) metastases. Any neurologic symptoms that developed either as a result of the brain metastases or their treatment must have resolved or be stable either, without the use of steroids, or are stable on steroids and/or anticonvulsants prior to the start of treatment.
18. History of active primary immunodeficiency.
19. Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), hepatitis B (known positive HBV surface antigen (HBsAg) result), hepatitis C. Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

20. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab. The following are exceptions to this criterion:
    a. Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection).
    b. Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent.
    c. Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication).
21. Receipt of live attenuated vaccine within 30 days prior to the first dose of IP. Note: Patients, if enrolled, should not receive live vaccine whilst receiving IP and up to 30 days after the last dose of IP.
22. Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of durvalumab monotherapy.
23. Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients.
24. Judgment by the investigator that the patient is unsuitable to participate in the study and the patient is unlikely to comply with study procedures, restrictions and requirements.

Investigational products, dose and mode of administration:

- Four courses of durvalumab 1500 mg IV day 1, carboplatin (AUC=5, Calvert's formula) IV day 1 and etoposide 100 mg/m^2 BSA IV day 1. On days 2-4, etoposide is administered in a dose of 100 mg/m^2 BSA IV or 200 mg/m^2 BSA PO. Chemoimmunotherapy courses are administered every three weeks. After completing four courses, durvalumab 1500 mg IV is given every four weeks until intolerable toxicity, patient's wish, or disease progression and need for other treatment.
- The dose of durvalumab will be adjusted to 20 mg/kg if a patient's body weight falls below 30 kg
- Patients randomized to the experimental arm will receive TRT of 30 Gy in 10 fractions, one fraction per day, 5 fractions per week, between the second and third chemo-immunotherapy course.
- Patients who achieve a response when evaluated after completion of chemo-immunotherapy may be offered PCI of 25 Gy in 10 fractions or 30 Gy in 15 fractions, one fraction per day, 5 fractions per week according to local treatment policy.

Safety assessments:

Toxicity will be classified according to CTCAE v5.0. Cognitive function will be assessed using the MoCA test. Patients will report HRQoL on the EORTC QLQ C30+LC13.

Efficacy assessments:

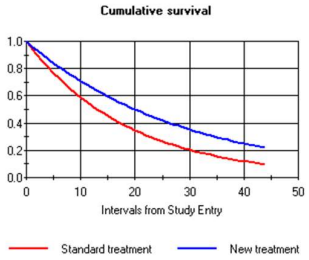
OS will be measured from the day of randomization until death by any cause, PFS from the day of randomization until RECIST 1.1 progression or death by any cause. Response to treatment and progression will be assessed according to RECIST 1.1. Response to treatment and progression will be assessed on CT and MRI scans at regular intervals. Sensitivity analyses including measurement of previously irradiated lesions (both thoracic lesions and brain metastases) will be performed.

Statistical methods and data analysis:

Cox proportional hazard method will be used to compare survival. The primary survival analyses will be performed 14 months after the last patient entry (to ensure that 1-year survival data are captured). Pearson's Chi-Square test will be used to compare toxicity, overall response rates, and treatment completion rates. Mann-Whitney's test will be used to compare number of completed chemo-immunotherapy- and durvalumab-courses.

Median OS will be estimated using the Kaplan-Meier method, and a Cox-model will be used for multivariable survival analysis adjusting for established prognostic factors in the target population (sex, PS, disease stage, presence brain metastases and liver metastases) and age. A separate analysis plan will be defined for the biomarker analyses.

Sample size determination:



The sample size calculation assumes an accrual period of 30 months and that the primary survival analysis is performed 14 months after last patient entry. Additional survival analyses will be performed 2, 3 and 4 years after last patient entry. All patients will be followed for a maximum of 5 years when the final survival analysis will be performed.

The calculation is based on a constant hazard ratio of 0.65, corresponding to median survival times of 13.10 months for the control group and 20.02 months for the experimental group, and 1-year survival rates of 53% in the control group and 66% in the experimental group.

This effect was selected as an effect of clinical relevance and an effect of this magnitude might be anticipated if there is a synergistic effect of combining radiotherapy with durvalumab. The criterion for significance (alpha) has been set at 5%. The test is 2-tailed, which means that an effect in either direction will be interpreted. For this study design, alpha and tails, the population effect size described above, and to have power of 80% to yield a statistically significant result, 128 patients are required in each treatment group.

Enrolment will continue until 128 or more patients in the control arm have completed minimum three chemo-immunotherapy courses, and minimum 128 patients in the experimental group have completed minimum three chemo-immunotherapy courses plus TRT of 30 Gy. We expect a loss to follow-up and inability to complete three courses (plus TRT in the experimental group) of maximum 15% and estimate that we need to enroll a total of 302 patients.

All eligible patients who are randomized will be included in the primary efficacy analyses (ITT-population). All patients who commence chemo-immunotherapy will be included in the toxicity analyses. In addition, we will perform analyses of the patients who complete minimum three chemo-immunotherapy courses (and TRT in the experimental arm) (per protocol population).

An independent Safety and data monitoring committee will perform an interim analysis when 2/3 of the target number of patients (n≥85 in both arms) have completed a minimum of three chemotherapy courses (and TRT in the experimental arm). According to the O'Brien-Fleming approach, an alpha of 0.0054 will be allocated to the interim analyses. Consequently, enrolment will be stopped if the survival difference is statistically significant with a 2-sided p≤0.0054. If enrolment continues beyond the interim analysis, the significance level for the primary survival analysis is p≤0.0492.

The sample size calculation was performed using SPSS Sample Power v3.

2. SCHEDULE OF STUDY ASSESSMENTS, PROCEDURES AND TREATMENT

Year	1										
Week	-4 to -1[ab]	0	3	3-4	3-4	6	9	11-12	13	13-15	17
	Screening	Durvalumab/ carboplatin/ etoposide 1	Durvalumab/ carboplatin/ etoposide 2	Response evaluation	Start of thoracic radiotherapy	Durvalumab/ carboplatin/ etoposide 3	Durvalumab/ carboplatin/ etoposide 4	Response evaluation	Durvalumab 5	Start of PCI	Durvalumab 6
Informed consent	X										
Eligibility criteria	X										
Medical history, demography, height, tobacco use	X										
Clinical examination/ performance status/weight	X	X	X			X	X	X	X		X
ECG[c]	X										
Concomitant medication	X							X	X		X
HRQoL (QLQ C30 + LC13)	X							X			
Cognitive function (MoCA)	X							X			
Clinical chemistry[de]	X	X	X			X	X		X		X
Hematology[f]	X	X[g]	X[g]			X[g]	X[g]				
Pregnancy test in women of childbearing potential[h]	X	X	X			X	X		X		X
Hepatitis B&C, HIV if suspected[i]	X										
Pulmonary function[j]	X							X			
Assessment of adverse events	X	X	X			X	X	X	X	X	X
CT thorax/upper abdomen[k]	X			X[l]				X			
MRI of the brain[k,m]	X							X			
Collection of tumor tissue[n]	X										
Blood biomarker analyses	X			X				X			X
Stool for biomarker analyses[o]	X			X				X			X
Randomization	X										

[a]Every effort should be made to minimize the time between start of screening and starting treatment.
[b]If laboratory or imaging procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes with consent of the patient provided they were obtained within 28 days of randomization.
[c]Any clinically significant abnormalities detected require triplicate ECG results.
[d]If screening clinical chemistry and hematology assessments are performed within 5 days prior to Day 1 (first infusion day of each course), they do not need to be repeated at Day 1.
[e]Bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, creatinine, sodium (Na), potassium (K), thyroid stimulating hormone (TSH), free thyroxine (FT4), erythrocyte sedimentation rate (ESR), glucose, lactate dehydrogenase (LDH). Tri-iodothyronine (T3) or FT4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.
[f]HgB, leukocytes, neutrophil granulocytes, and platelets
[g]On day 1 and 10 of each chemotherapy course.

[h]For women of childbearing potential only. A urine or serum pregnancy test is acceptable. Women of childbearing potential are required to have a pregnancy test within 7 days prior to the first dose of study drugs and then before every durvalumab course. Pregnancy test may occur on Day 1, but results must be available and reviewed by the treating physician or Investigator prior to commencing an infusion.
[i]Hepatitis B surface antigene (HBsAg), Hepatitis B core antibody (HBcAb), and Hepatitis C antibody (HCV Ab) tests are mandatory. If a patient has a negative HBsAg test and a positive HBcAb test, an HBV DNA test must be performed to determine if the patient has an HBV infection. If a patient has a positive HCV Ab test, an HCV RNA test must be performed to determine if the patient has an HCV infection.
[j]FEV1, FEV1%, FVC, FVC%, and DLCO%
[k]RECIST assessments will be performed on images from CT of the chest and upper abdomen and MRI of the brain, each preferably with IV contrast. Additional anatomy should be imaged based on signs and symptoms of individual patients at baseline and follow-up. Confirmation of response is not mandatory. If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their next scheduled visit.
[l]CT scan for radiotherapy planning may be used for patients in the experimental arm. A regular CT scan should be performed for patients in the control arm at the same time as CT scans for radiotherapy planning would be performed, usually 3-4 weeks after the first day of the first chemo-immunotherapy course.
[m]May be replaced with CT if MRI is unavailable.
[n]Archival diagnostic material or re-biopsy for confirmation of suspected relapse.
[o]Not mandatory.

Year	**1**				**2**					
Week	**21**	**29**	**37**	**45**	**1**	**9**	**17**	**25**	**33**	**41**
Durvalumab	Durvalumab every 4 weeks until progressive disease and need for other treatment, unacceptable toxicity or patients wish to discontinue									
Clinical examination/ performance status/weight	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X
HRQoL (QLQ C30 + LC13)	X	X	X	X	X		X		X	
Cognitive function (MoCA)	X				X					X
Clinical chemistry[e]	X	X	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X	X	X
Pregnancy test in women of childbearing potential[h]	Before every durvalumab course									
Assessment of adverse events	X	X	X	X	X	X	X	X	X	X
CT thorax/upper abdomen[k]	X	X	X	X	X	X	X	X	X	X
MRI of the brain[k,m]	(X)[o]	X	(X)[o]	X	(X)[o]	X	(X)[o]	X	(X)[o]	X
Blood for biomarker analyses		X			X					
Stool for biomarker analyses[o]		X			X					

Year		3				4				5				Progressive disease or patient lost to follow-up
Week	**49**	**10**	**23**	**36**	**49**	**10**	**23**	**36**	**49**	**10**	**23**	**36**	**52**	
Clinical examination/ performance status/weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HRQoL (QLQ C30 + LC13)	X													X
Cognitive function (MoCA)					X				X				X	X
Clinical chemistry[e]	X													X
Hematology[f]	X													X
Assessment of adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CT thorax/upper abdomen[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MRI of the brain[k,m]	(X)[o]	X	(X)[o]	X	(X)[o]	X	(X)[o]	X	(X)[o]	X	(X)[o]	X	(X)[o]	X
Blood for biomarker analyses	X				X				X					X
Stool for biomarker analyses[o]	X				X				X					X
Biopsy of progressing lesion[o]														X

Follow-up for patients who have completed study treatment: According to the study schedule.

Follow-up of patients who have discontinued study treatment due to other reasons than RECIST 1.1 progressive disease (PD) and need for other treatment: Should be followed according to the study schedule until RECIST 1.1 PD and need for other treatment.

Assessments at RECIST 1.1 PD: All evaluations and assessments listed in the last column of the study schedule ("PD") should be performed when disease progression occurs. If any assessment has been performed within the last 7 days, they do not need to be repeated, but it is essential that all assessments are performed (stool sampling and re-biopsy are not mandatory).

Follow-up for patients beyond RECIST 1.1 PD: As long as patients are considered to benefit clinically from continuing study treatment and are not in need for other systemic treatment, they can continue study treatment. This usually applies for patients who have completed chemoimmunotherapy and receive durvalumab monotherapy. A confirmatory CT evaluation should be performed within 4-6 weeks to ensure that they do not experience rapid disease progression requiring other therapy. At a minimum, subsequent intervals between CT evaluations should be according to the study schedule.

Follow-up for patients who discontinue study treatment due to RECIST 1.1 PD: Post-study AEs/SAEs should be reported according to protocol. Post-study treatment and survival must be recorded. Patients will be followed and treated according to local routines.

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3. ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this clinical study protocol.

Abbreviation or term	Explanation
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BSA	Body surface area
CI	Confidence interval
CL	Clearance
CNS	Central nervous system
CR	Complete response
CT	Computed tomography
CTLA-4	Cytotoxic T-lymphocyte-associated antigen-4
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDTA	Disodium edetate dihydrate
ES	Extensive stage
FFPE	Formalin fixed paraffin embedded
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Conference on Harmonization
ICI	Immune checkpoint inhibitor
ICRU	International Commission on Radiation Unit and Measurements
IEC	Independent Ethics Committee
IgG	Immunoglobulin
ILD	Interstitial lung disease
imAE	Immune-mediated adverse event
IRB	Institutional Review Board
IV	Intravenous(ly)
LS	Limited stage
mAb	Monoclonal antibody
MoCA	Montreal Cognitive Assessment
miRNA	Micro ribonucleic acid
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid

Abbreviation or term	Explanation
MTD	Maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	Non-small cell lung cancer
OR	Objective response
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PCI	Prophylactic cranial irradiation
PD	Progressive disease
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PFS	Progression-free survival
PR	Partial response
PRO	Patient reported outcome
QTc	Time between the start of the Q wave and the end of the T wave corrected for heart rate
QTcF	QT interval on ECG corrected using the Frederica's formula
REB	Research Ethics Board
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RT	Radiotherapy
SAE	Serious adverse event
SCLC	Small-cell lung cancer
SD	Stable disease
SoA	Schedule of assessments
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TIL	Tumor infiltrating lymphocyte
TRT	Thoracic radiotherapy
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
WBRT	Whole brain radiotherapy
WHO	World Health Organization

4. Introduction

4.1 Disease background

4.1.1 Lung cancer

Lung cancer is the deadliest cancer, causing more years of life lost than the other three most common cancers altogether (breast, prostate and colon cancer).[1,2] More than 3300 are diagnosed with lung cancer every year in Norway, and 2200 die from the disease, accounting for more than 5% of all deaths.[3]

Small-cell lung cancer (SCLC) accounts for 13-15% of lung cancer cases.[3,4] Untreated, the prognosis is poor (2-4 months) since SCLC grows more rapidly and metastasizes more frequently than other types of lung cancer. Due to the aggressive biology, it has been estimated that SCLC causes 4% of all cancer related deaths.[5]

4.1.2 Treatment of SCLC

Patients with localized disease (T1-2N0) are offered surgery followed by adjuvant chemotherapy and/or radiotherapy and prophylactic cranial irradiation, but very few (approx. 5 per year in Norway) are operable since most have regional or metastatic disease at the time of diagnosis.[6-8] For inoperable patients, chemotherapy is the main treatment, and platinum/etoposide remains the standard regimen, at least in the western world.[9] A Japanese trial showed that platinum/irinotecan was superior to platinum/etoposide in ES SCLC, but the relatively large survival benefit was not confirmed in trials performed in other countries.[10-12] A possible explanation is differences in pharmacogenomics.[13] A meta-analysis showed a small benefit of platinum/irinotecan over platinum/etoposide in terms of survival but was mainly driven by Asian studies.[14] Thus, platinum/etoposide remains the standard regimen in the Western world.[9]

Concurrent chemotherapy and TRT is superior to chemotherapy alone when all lesions can be included in a RT field (limited stage, "LS SCLC").[15] Chemotherapy alone has until recently been the standard treatment for patients with more widespread disease (extended stage, "ES SCLC").[9] Prophylactic cranial irradiation (PCI) reduces the frequency of brain metastases and prolongs survival in LS patients who respond to the primary treatment.[16] The role of PCI is more debated in patients with ES. One European study showed that PCI reduces the risk of brain metastases and prolongs survival in this setting,[17] while a Japanese study did not confirm the survival benefit, suggesting that active surveillance is a better approach than PCI.[18]

Up to 90% of LS patients respond and 25-30% are cured by chemoradiotherapy and are alive after 5 years.[19,20] The response rate is lower for ES SCLC (approx. 65%), almost all patients relapse within 1-2 years, and the 5-year survival is around 3%.[5] There have been major improvements in treatment outcomes for NSCLC, but the survival rates for SCLC have remained more or less unchanged the last 20 years.[2,21]

One reason for the lack of progress is that most lung cancer research focuses on NSCLC. At the ASCO annual meeting 2020, 6300 abstracts were submitted. Of these, 512 reported lung cancer research, but only 22 (4.3%) concerned SCLC. The poor survival, the low 5-year survival, the lack of progress, research and new therapies for SCLC underscores the need for research on this orphaned disease.

4.2 Immunotherapies

It is increasingly understood that cancers are recognized by the immune system, and, under some circumstances, the immune system may control or even eliminate tumors.[22] PD-L1 is part of a complex system of receptors and ligands that are involved in controlling T-cell activation.[23] When PD-L1 binds to PD-1, an inhibitory signal is transmitted into the T-cell, which reduces cytokine production and suppresses T-cell proliferation. Tumor cells exploit this immune checkpoint pathway as a mechanism to evade detection and inhibit immune response. PD-L1 is expressed in a broad range of cancers, and it is well established that anti–PD-L1 and anti PD-1 antibodies have clinical activity and a manageable safety profile in a wide range of cancers, including lung cancer.[24-26]

4.2.1 Durvalumab

Durvalumab is a human monoclonal antibody (mAb) of the immunoglobulin G (IgG) 1 kappa subclass that inhibits binding of PD-L1 and was developed by AstraZeneca/MedImmune for use in the treatment of cancer. The proposed mechanism of action is interference in the interaction of PD-L1 with PD-1 and CD80 which releases the inhibition of immune responses to tumor cells.

To date durvalumab has been given to more than 8000 patients as part of ongoing studies either as monotherapy or in combination with other anti-cancer agents. Details on the safety profile of durvalumab monotherapy are summarized in 4.5.2. The current durvalumab Investigator's Brochure (IB) contains a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics.

4.2.2 Immunotherapies in lung cancer

For lung cancer patients, immune checkpoint inhibitor (ICI) therapy was first established for NSCLC and is now standard therapy as monotherapy and combined with cytotoxic chemotherapy - as first line and relapse treatment in metastatic disease, and as consolidation therapy after concurrent chemoradiotherapy for stage III disease.[24-27]

4.2.3 Immunotherapy in SCLC

The first signals of an effect of immune checkpoint inhibitors (ICIs) in SCLC came from phase I/II studies. One third of patients with pre-treated SCLC (n=24) had an objective response from pembrolizumab.[28] In a randomized phase II trial, pre-treated SCLC patients achieved an objective response rate of 23% and a median survival of 7.7 months after receiving nivolumab plus ipilimumab.[29] Later, a phase II study showed antitumor activity of durvalumab in pre-treated ES SCLC patients,[30] and two phase II studies showed activity of durvalumab plus tremelimumab in pre-treated ES SCLC.[31,32]

Promising results from early phase studies led to the initiation of several larger studies of checkpoint inhibitors in ES SCLC (monotherapy, combinations with other checkpoint inhibitors or chemotherapy), both in the first line setting, as maintenance therapy after primary chemotherapy and in previously treated patients. Furthermore, several studies of immunotherapy concurrently or after chemoradiotherapy in LS SCLC are ongoing.

Most studies of ICIs in NSCLC are positive, but several studies of ICIs in SCLC have been negative. In a phase II trial of patients who had progressed after first-line platinum-doublet chemotherapy, patients were randomized to receive atezolizumab monotherapy or chemotherapy. Atezolizumab resulted in significantly inferior response rate and median PFS.[33]

In a phase III trial, ES SCLC patients with non-progression after first-line platinum-chemotherapy were randomized to placebo, nivolumab monotherapy or nivolumab plus ipilimumab. There was no significant benefit in OS of neither nivolumab monotherapy (median OS 10.4 vs. 9.6 months; HR 0.84, 95% CI 0.7-1.0), or nivolumab plus ipilimumab (9.2 vs. 9.6 months; HR 0.92, 95% CI 0.8-1.1; p=0.37).[34]

Another phase III trial randomized patients with recurrent SCLC to receive nivolumab monotherapy or chemotherapy (topotecan or amrubicin). There was no significant benefit in OS (7.5 vs. 8.4 months; HR 0.86, 95% CI 0.71-1.04; p=0.11).[35]

4.2.4 Combined chemotherapy and immunotherapy as first-line treatment of ES SCLC

Two recent studies have established ICIs in the treatment of ES SCLC. Both compared chemotherapy plus a PD-L1 inhibitor with chemotherapy alone. In the Impower 133 trial, patients were randomized to four courses of carboplatin/etoposide with atezolizumab or placebo. There was a significant benefit in terms of median OS (12.3 vs. 10.3 months; p=0.007) and median PFS (5.2 vs. 4.3 months; p=0.02).[36]

In the CASPIAN trial, patients were randomized to receive four courses of platinum plus etoposide plus durvalumab or durvalumab plus tremelimumab, or up to six courses of platinum plus etoposide. The durvalumab-combination provided a significant benefit in terms of survival compared with platinum plus etoposide alone (13.0 vs. 10.3 months; p=0.0047), which numerically was similar to what was observed in Impower 133. The addition of tremelimumab did not significantly improve the efficacy of durvalumab.[37]

A third trial combining chemotherapy with an ICI was published this summer. In the KEYNOTE-604,

patients were randomized to receive platinum/etoposide plus pembrolizumab or placebo. There was a significant prolongation of PFS (HR 0.75; p=0.0023) and a prolongation of OS (HR 0.80; p=0.0164). The difference in survival did, however, not reach the pre-specified threshold of p=0.0128. Numerically, the median OS was lower than in the CASPIAN and Impower 133; 10.8 months in the pembrolizumab arm, and 9.7 months in the placebo arm.[38] In all these trials, adding an ICI was well tolerated.

These three studies show that combining chemotherapy with an ICI is the new standard first-line regimen for ES SCLC, and that durvalumab and atezolizumab are the ICIs of choice. The benefit in terms of median OS is, however, limited (2.0 and 2.7 months), The survival curves do not split until after 6 months after start of treatment. Whether adding an ICI provides a long-term survival, similar to what have been observed in studies of advanced NSCLC, is unknown due to the short follow-up time.

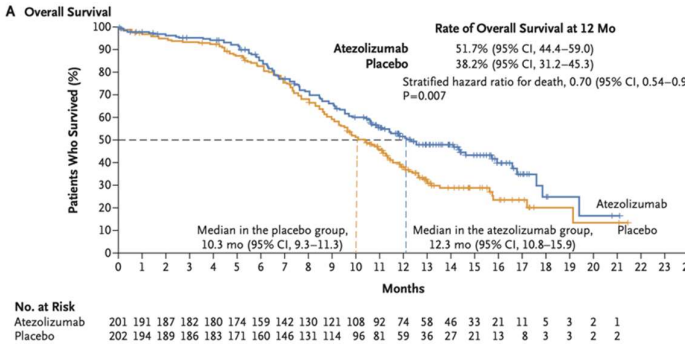


Figure 2a Overall survival curves from the Impower 133 trial

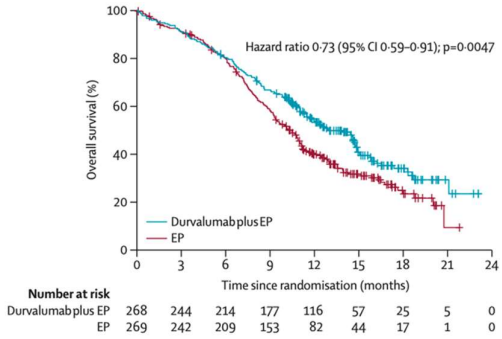


Figure 2b Overall survival curves from the CASPIAN trial

4.2.5 Predictive biomarkers

The most relevant biomarkers for predicting response to ICIs are PD-L1 expression and TMB. However, the predictive role of these markers appears to be insignificant in SCLC.

PD-L1 expression was assessed in KEYNOTE 604. The proportion of PD-L1 positive was lower than in NSCLC (approx. 40% vs. 65%), and PD-L1 expression was not associated with response to pembrolizumab.[38] TMB was assessed in Impower 133, and the efficacy was similar regardless of TMB.[36] Thus, there are no established predictive factors for ICIs in SCLC.

4.2.6 Paraneoplastic neurological syndrome (PNS) in SCLC

3-5% of patients with SCLC have a paraneoplastic neurological syndrome (PNS) syndrome,[39] which is more frequent than in most other solid tumors. Due to the neuroectodermal origin of the cells that form SCLC, they share expression of many peptides only found in the brain. As the blood-brain barrier diminishes the extent and efficacy of the patrolling qualities of our own immune system, antigens expressed by SCLC and the brain alone are less vigorously recognized as body-self. Normally, cells producing antibodies aimed at body-self antigens would directly go into apoptosis, without ever entering the blood stream. The combination of an aggressive anti-tumor response in combination with the limited recognition of brain antigens can therefore easily lead to auto-antibody formation. These auto-antibodies can then try to control the SCLC, while at the same time inducing a PNS as a side-effect.[40]

SCLC-patients with PNS have consistently shown an improved overall survival, probably due to a better tumor control.[41-43] These patients are thought to have an inflamed anti-tumor micro-environment with an increase of CD3-, CD4- and CD8- T-cell infiltrates. An improvement in median overall survival of up to 6 months, and an increased tail of long-term survivors have been observed (up to 30% alive after 2 years).[41]

A far larger proportion of asymptomatic SCLC patients has one or several auto-antibodies aimed against neuronal proteins, and approximately 40% of SCLC patients have low titer antibodies against SOX1 or HuD,[41] and when including combinations of other auto-antibodies (e.g. anti-CV2, anti-recoverine, anti-Zic4,[44] anti-VGCC,[45] Trim46[46] or anti-KCTD16[47]) this proportion increases to >50%.

Whether subclinical autoantibodies are associated with survival in SCLC patients is unclear. Some

studies show that they are associated with improved survival, while others have not found such associations. As the effects of anti-PD-L1 therapy vary considerably among SCLC patients, it seems reasonable to investigate whether the immune system is linked to response to such treatment, especially whether a propensity to develop auto-antibodies increases the chance of responding to immune checkpoint inhibitor therapy. One clue supporting this possibility is our observation that patients who developed an antibody-mediated paraneoplastic neurological syndrome, like anti-GABAbR encephalitis, during PD-(l)1 treatment had a prolonged good anti-tumor response at the same time.

4.2.7 TRT in ES SCLC

A randomized phase III trial showed that TRT improves PFS in ES SCLC (HR 0.73, p=0.001), and the PFS curves split immediately after administering TRT. The study did not, however, meet the primary endpoint of improved 1-year survival in the overall population (33% vs. 28%, p=.066), but there was a significant benefit in terms of 18-months (16% vs 9%, p=0.03) and 24-months survival (13% vs. 3%, p=0.004). Among patients with residual thoracic disease after chemotherapy, there was a significant improvement in OS (HR .81, p=0.044). Thus, the role of TRT has been debated, and is not routinely offered in Scandinavia, and was not allowed in the CASPIAN or Impower 133.[48]

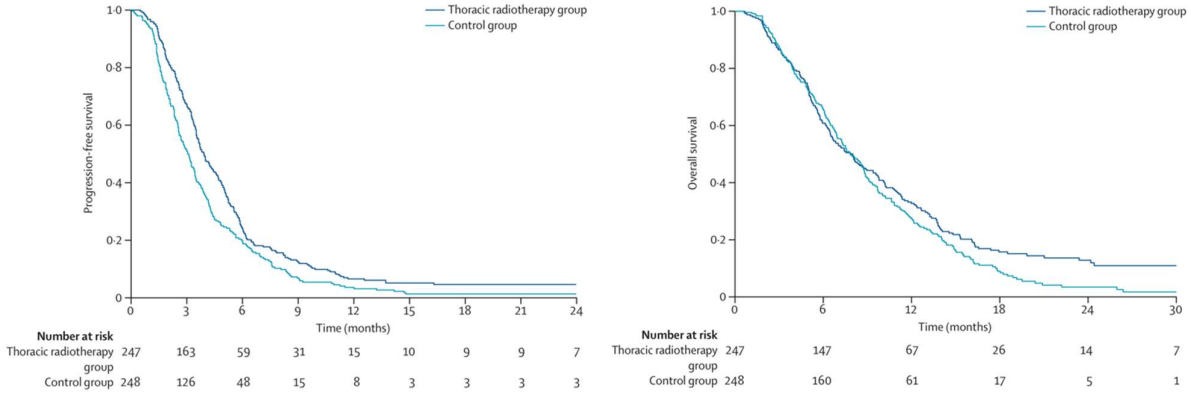


Figure 3 Progression free survival and overall survival curves from the trial of TRT in ES SCLC (CREST).

4.2.8 Synergistic effect of combining RT and immunotherapy

RT has traditionally been considered to be a local treatment, mainly affecting the targeted tumor cells. There are reports of an abscopal effect, i.e. treatment response on lesions outside the RT fields, but these reports are few in numbers.[49]

There are, however, reasons to believe that there is a synergistic effect of concurrent RT and immune checkpoint inhibitor therapy that are of more clinical relevance. In addition to the direct cytotoxic effect on tumor cells, RT may also change the tumor microenvironment in a way that may promote an improved systemic effect of checkpoint inhibitors. It has been shown that RT induce upregulation of tumor surface MHC-I and PD-L1 expression, increase the proportion of beneficial TILs and their effector activity, drive polyclonal T-cell responses, which may create a suitable neoantigen repertoire. On the other hand, RT may also attract immunosuppressive cells.[50-54]

Though there are reasons to believe that combining RT and immunotherapy improves efficacy of the systemic treatment, it is not yet established how to optimally combine these therapies. It appears that concurrent administration or administration of immunotherapy immediately after RT is the most effective approach.[27,52]

Combining immunotherapy and RT in lung cancer, including ES SCLC, appears to be safe,[55,56] but even if there is a lot of interest in investigating the potential synergistic effect, there is hitherto no results from randomized trials confirming that the combination results in a clinically relevant improved effect. In a recent publication, patients with head and neck squamous cell carcinomas randomized to receive stereotactic body RT to one lesion, did not experience a higher effect of concurrent nivolumab treatment. However, the study was small (n=62), and the results are not necessarily applicable to ES SCLC.[57]

4.2.9 Prophylactic cranial irradiation in ES SCLC

Whether PCI is beneficial for patients who receive combined immunotherapy and chemotherapy is unknown. It is unknown whether receiving checkpoint inhibitor therapy increases the potential detrimental cognitive effect of PCI, and the benefit of PCI may be reduced due to improved disease control due to the improved efficacy of the triple combination.

The only available data on PCI in patients receiving ICI, are from a subgroup analysis of the 44 patients who received PCI as part of the Impower 133 trial. There were no indications of more side effects among those who received PD-L1 inhibitor therapy, but the cohort was small and follow-up did not include assessment of long-term neurocognitive decline.[58]

4.3 Research hypotheses

The main hypothesis is that adding TRT to chemotherapy plus durvalumab provides a survival benefit for patients with extensive stage (ES) small-cell lung cancer (SCLC). Specifically, we hypothesize that:

- combining TRT, chemotherapy and durvalumab is feasible and well tolerated
- adding TRT improves 1- and 2-year survival, median OS, response rates, and PFS
- the patients who benefit the most from the study treatment can be identified through analyses of tissue, blood and stool samples
- PCI is well tolerated, reduces the risk of brain metastases and prolongs survival in ES SCLC patients who receive chemotherapy plus durvalumab compared with patients who do not receive PCI

4.4 Rationale for conducting this study

- Chemotherapy plus an PD-L1 inhibitor is considered a new standard of care for first-line treatment of ES SCLC but is not yet available/reimbursed in all countries. Durvalumab plus platinum/etoposide is one of these new standard regimens. However, the survival benefit is limited, especially for the first 6 months, and a more effective treatment is needed.
- A more effective initial therapy might improve survival the first 6 months and long-term survival.
- It has been demonstrated that TRT improves survival in ES SCLC, and the effect in terms of PFS is immediate.
- Several studies suggest a synergistic effect of combining RT and ICI. Concurrent administration appears to be the most effective approach, and we will administer the TRT between the second and third chemoimmunotherapy courses. This is deemed to be the earliest time point that TRT may be administered at all sites. We know that SCLC patients may achieve a substantial response to one chemotherapy course *(Halvorsen, 2016)* and believe that administering TRT earlier than in the CREST trial will make it easier to locate the target lesions, increases the likelihood of irradiating viable tumor cells, and consequently increase the chance for achieving a synergistic effect of the TRT and the immunotherapy - and not merely an additive effect.
- Combining high-dose TRT, platinum doublet chemotherapy and ICI appears to be well tolerated. Thus, combining medium dose TRT with durvalumab and carboplatin/etoposide should be feasible and well tolerated. However, since there is no data on this combination, investigating whether ading TRT increases the frequency or severity of side effects is an essential part of this trial.
- The benefits and tolerability of PCI in ES SCLC patients receiving chemotherapy plus ICI are unknown. We will compare the timing and frequency of brain metastases between patients who receive PCI and those who do not. Furthermore, we will measure and compare cognitive function before and after PCI.
- The survival benefit from adding ICI does not appear before after 6 months. Thus, we restrict the protocol for patients in performance status 0-1. In a previous trial on chemotherapy in ES SCLC, median OS was below 6 months among patients with a PS of 2 or more.
- The optimal length of durvalumab treatment remains to be defined since there is limited data on the long-term benefit of checkpoint inhibitors in ES SCLC. Thus, durvalumab treatment will continue until PD and need for other treatment, unacceptable toxicity or patients wish to discontinue.
- There is very limited knowledge of prognostic and predictive biomarkers in SCLC in general and for ICI therapy specifically since few have conducted such research and the markers established for other

types of cancer appears to be of little relevance in SCLC. We will collect tumor, blood and stool for translational research aiming at characterizing patients who benefit the most from the study therapy.
- SCLC patients with paraneoplastic neurological syndrome (PNS) syndrome and asymptomatic patients with autoantibodies against neuronal proteins may have a better and more prolonged response to ICIs. We will investigate whether there are associations between the presence and type of autoantibodies and long-term benefit of the study therapy.

4.5 Benefit/risk and ethical assessment

4.5.1 Potential benefits

The potentially improved disease control from adding TRT to the systemic treatment is the most important potential benefit for the participants. For patients with such an aggressive disease as SCLC, prolonged disease control is of outmost importance, as this improves quality of life, maintains functional level, and prolongs survival time. For the health care system, better disease control will reduce the need for resources required to provide optimal care and support.

Hitherto, all SCLC patients are treated equally, though we know from experience that there is a large heterogeneity with respect to treatment response, response duration, symptom development and survival time.[19,59] Our knowledge of prognostic and predictive biomarkers in SCLC is in general very limited. The planned translational research may lead to a novel classification system based on molecular markers, with potentially large impacts for both patients and the health care systems.

A classification system will enable us to avoid ineffective, unnecessary, potentially toxic therapy, and patients will avoid spending time for futile therapy. Scientifically, the impact of an improved classification is huge, as it allows for more targeted enrolment in trials that will improve the relevance, feasibility and quality of future research. Targeted enrolment allows for reduced sample sizes, shorter readout time, reduced costs, and increased number of trials that can be conducted.

4.5.2 Overall risks of durvalumab

Monoclonal antibodies directed against immune checkpoint proteins aim to boost endogenous immune responses directed against tumor cells. By stimulating the immune system however, there is the potential for adverse effects (AEs) on other tissues.

Most adverse drug reactions seen with ICIs are due to the effects of inflammatory cells on specific tissues. These immune mediated effects can occur in nearly any organ system and are most commonly seen as gastrointestinal AEs such as colitis and diarrhea, pneumonitis/interstitial lung disease (ILD), hepatic AEs such as hepatitis and liver enzyme elevations, skin events such as rash and dermatitis and endocrinopathies including hypo- and hyper-thyroidism.

Risks with durvalumab include, but are not limited to, diarrhea/colitis pneumonitis/ILD, endocrinopathies (hypo- and hyper-thyroidism, type I diabetes mellitus, hypophysitis and adrenal insufficiency) hepatitis/increases in transaminases, nephritis/increases in creatinine, pancreatitis/increases in amylase and lipase, rash/pruritus/dermatitis, myocarditis, myositis/polymyositis, thyroiditis, pemphigoid, myasthenia gravis, immune thrombocytopenia, and other rare or less frequent inflammatory events including neurotoxicities, infusion-related reactions, hypersensitivity reactions, and infections/serious infections.

In monotherapy clinical studies, most common AEs (all grades) (≥ 15% of patients) are fatigue, nausea, decreased appetite, dyspnea, cough, constipation, diarrhea, vomiting, back pain, pyrexia, asthenia, anemia, arthralgia, peripheral edema, headache, rash, and pruritus. Approximately 9.4% of patients experienced an AE that resulted in permanent discontinuation of durvalumab and approximately 6.5 % of patients experienced a serious adverse event (SAE) that was considered to be related to durvalumab. For information on all identified and potential risks with durvalumab, please refer to the current version of the durvalumab IB.

Most of the treatment-related AEs were manageable with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated side-effect.

Overall, adding durvalumab to platinum/etoposide chemotherapy in the CASPIAN trial did not

increase the frequency or severity of AEs. The proportion who experiences grade 3-4 toxicity was 62% both among patients who received chemoimmunotherapy and in the control arm. Immune-related AEs occurred in 20% of patients in the durvalumab-arm. Of these, 12/265 (5%) experienced grade 3 or 4 AEs, and one patient died from immune related hepatotoxicity.[37]

In a small phase I/II study, 10 patients on durvalumab received palliative RT. There were no severe RT-related AEs.[60] A phase II trial (n=40) of concurrent chemoradiotherapy to 60-66 Gy and the PD-L1 inhibitor atezolizumab in unresectable NSCLC, did not reveal any indications of increased RT toxicity compared with historical data.[56] In the PACIFIC trial, consolidation durvalumab therapy was well tolerated in patients who did not progress after chemoradiotherapy in locally advanced NSCLC.[27] Overall, there are currently no clinical data suggesting that combining chemoimmunotherapy with low-dose TRT causes severe radiotoxicity.

4.5.3 Overall benefit-risk

Results from the CASPIAN trial shows that durvalumab plus platinum/etoposide chemotherapy is well tolerated and prolongs survival. TRT is well tolerated in ES SCLC patients, and studies suggest that concurrent chemo-immunotherapy and TRT is well tolerated in NSCLC. On this basis, we believe that the overall risk is low, and that the experimental therapy may provide a clinically relevant survival benefit for an important group of patients in desperate need for better therapies.

5. Provide summary of overall benefit-risk for the study objectives

5.1 Primary objective(s)

We consider survival the most relevant endpoint for ES SCLC patients. Since we will irradiate lesions in the experimental arm, there are potential methodological issues with using PFS as the primary outcome, since the RECIST criteria consider irradiated lesions non-measurable. Survival may be influenced by post-study therapy, but there is little variation in relapse therapy for ES SCLC. All post-study therapy will be registered.

There is currently no data suggesting whether the combination therapy may provide a synergistic effect or an additive effect. Thus, it is difficult to predict how the PFS-curves may be influenced by adding TRT, and it is consequently difficult to select the most appropriate PFS-endpoint.

In conclusion, we consider 1-year overall survival to be the most appropriate endpoint, it is easily measured, and provides a strong and clinically relevant measure of the potential effect of the experimental therapy. There is no risk associated with this measure.

5.1.1 Secondary objective(s)

In general, the major benefit of ICIs in cancer treatment is that some patients achieve long term survival. Thus, we plan a follow-up of 5 year after last patient entry to accurately assess whether some patients achieve a long term survival. Follow-up time in completed trials of chemo-immunotherapy in ES SCLC was designed with a too short follow-up time to assess survival beyond 2 years.

Current data shows that high-dose TRT can safely be administered concurrently with chemotherapy and checkpoint inhibitors, but we cannot rule out that TRT adds significant toxicity in patients with ES-SCLC. Thus, we will compare frequency and severity of adverse events, as well as patient-reported health-related quality of life, between treatment arms.

PFS may be difficult to accurately assess (see above), but is still of interest, especially when it comes to local control. We assume that adding TRT improves local control, but if there is a synergistic effect of combining RT and durvalumab, the course of disease may also be altered. Thus, assessing the location and timing of metastases is of great interest. Furthermore, a synergistic effect should improve response rates, and to further investigate whether such an effect occurs, we will compare response rates in non-irradiated lesions (i.e. all non-irradiated lesions in the experimental arm compared with overall response rate in the control arm). The role of PCI in ES SCLC is debated. If adding TRT improves efficacy of chemoimmunotherapy, the value of PCI may be small. On the other hand, one can also imagine that TRT plus chemoimmunotherapy improves systemic disease control, and that brain metastases represent a major site for treatment failure.

5.2 Exploratory objective(s)

If there is a synergistic effect of TRT and chemoimmunotherapy, the frequency of brain metastases may decrease in the experimental arm, or the time until brain metastases occur may be prolonged. Thus, we will compare the frequency and timing of brain metastases. To explore potential benefits or disadvantages of PCI, we will measure cognitive function before and after chemoimmunotherapy and PCI.

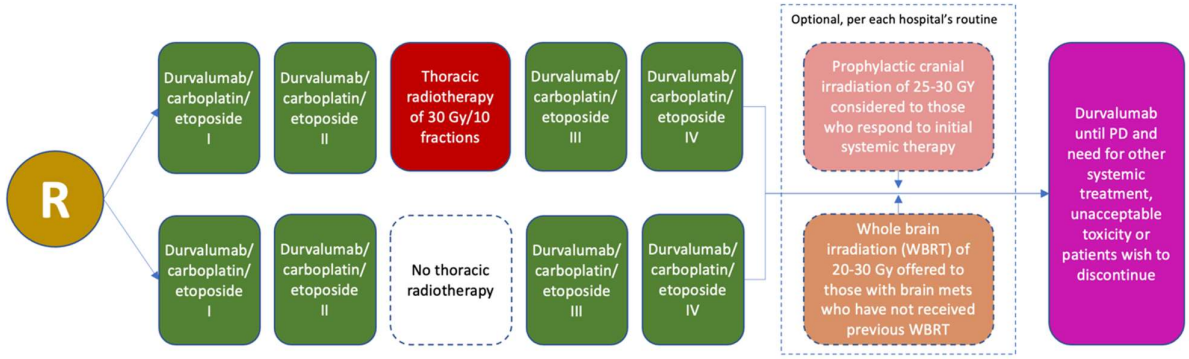
It is evident that not all ES SCLC patients benefit from durvalumab. Costs of new therapies has become an increasingly important issue. Identifying those who benefit the most from each therapy, will enable us to better individualize therapy for each patient. There are several benefits for both patients and society. Patients will avoid spending time for futile therapy, avoid unnecessary toxicity, and may be offered other, more effective treatments. More targeted therapy will reduce costs, but also better use of our health services' resources. Thus, the biomarker analyses may have significant implications for future clinical practice and research.

6. Study design

6.1 Overview of study design

International, randomized phase III trial. Patients will be randomized 1:1 stratified for established prognostic factors (presence of brain metastases, and presence of liver metastases) to receive chemoimmunotherapy plus TRT or chemoimmunotherapy alone.

Figure 1 Study flow chart



6.2 Study oversight for safety evaluation

A Data and safety monitoring committee (DSMC) will monitor the incidence and nature of all SAEs when 5, 15 and 30 patients have received 3 or more courses of chemoimmunotherapy and TRT and then every 6 months until all patients have completed study treatment to ensure patient safety. The members of the DSMC will be experienced clinicians and a statistician. Following each data review, the DSMC will provide recommendations to the Chief Investigator as to whether the study should continue or be amended, or whether the study should be stopped due to safety concerns (i.e., evidence of harm). The Chief Investigator will, together with the National Coordinating Investigators, make decisions on the basis of the DSMC recommendations. Any outcomes of these safety reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of the IRB/REB/IECs.

7. Patient selection

7.1 Inclusion criteria

For inclusion in the study patients must fulfill all the following criteria:

1. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. Written informed consent and any locally required authorization (eg, Health Insurance Portability and Accountability Act in the US, European Union [EU] Data Privacy Directive in the EU) obtained from the patient/legal representative prior to performing any protocol-related procedures, including screening evaluations.

2. Age ≥ 18 years at time of study entry.
3. ECOG performance status of 0 or 1.
4. Body weight >30 kg.
5. Adequate normal organ and marrow function as defined below:
   - Haemoglobin ≥10.0 g/dL.
   - Absolute neutrophil count (ANC) ≥1.5 × 10^9 /L.
   - Platelet count ≥100 × 10^9/L.
   - Serum bilirubin ≤1.5 x institutional upper limit of normal (ULN). This does not apply to patients with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of hemolysis or hepatic pathology).
   - ALT (SGPT) ≤2.5 x ULN unless liver metastases are present, in which case it must be ≤5 x ULN.
   - Measured creatinine clearance (CL) >40 mL/min or Calculated creatinine CL>40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance:

     Males Creatinin-clearance (mL/min) = $\frac{\text{Weight (kg) x (140 – age)}}{\text{72 x serum creatinine (mg/dL)}}$

     Females Creatinin-clearance (mL/min) = $\frac{\text{Weight (kg) x (140 – age)}}{\text{72 x serum creatinine (mg/dL)}}$ x 0.85
6. Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow-up.
7. Life expectancy of at least 3 months.
8. At least 1 lesion in the thorax, not previously irradiated, that qualifies as a RECIST 1.1 target lesion (TL) at baseline and is possible to irradiate to 30 Gy in 10 fractions. Tumor assessment by computed tomography (CT) scan or magnetic resonance imaging (MRI) must be performed within 28 days prior to randomization.
9. Histologically or cytologically confirmed SCLC. Mixed histology may be acceptable as long as the SCLC component accounts for more than 90%.
10. Stage IV disease according to the TNM v8. Patients with stage III disease are eligible if the disease is too widespread to be treated as LS SCLC.
11. Pulmonary function: FEV1 >1 L or >30 % of predicted value and DLCO >30 % of predicted value.
12. Female patients of childbearing potential (postmenarcheal, not postmenopausal [>12 continuous months of amenorrhea with no identified cause other than menopause], and no surgical sterilization) should use highly effective contraception and take active measures to avoid pregnancy while undergoing systemic study therapy and for at least 5 months after the last dose.
13. Patients with brain metastases are eligible provided they are asymptomatic or treated and stable on steroids and/or anticonvulsants prior to start of treatment.

7.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

1. Participation in another clinical study with an investigational product during the last 30 days.
2. Concurrent enrolment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study.
3. Previous chemo- or radiotherapy for SCLC. Patients who have undergone surgery, but no adjuvant therapy are eligible.
4. Any unresolved toxicity NCI CTCAE Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria.
5. Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the Chief Investigator.

6. Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab may be included only after consultation with the Chief Investigator.
7. Any concurrent chemotherapy, investigational product or biologic cancer therapy.
8. Any prior checkpoint inhibitor therapy, including durvalumab.
9. Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of study drugs.
10. Immediate need for thoracic radiotherapy or bulky disease outside the thorax, or need for such radiotherapy before completion of chemo-immunotherapy
11. Major surgical procedure within 28 days prior to the first dose of study drugs. Note: Local surgery of isolated lesions for palliative intent is acceptable.
12. History of allogenic organ transplantation.
13. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). The following are exceptions to this criterion:
    a. Patients with vitiligo or alopecia.
    b. Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement.
    c. Any chronic skin condition that does not require systemic therapy.
    d. Patients without active disease in the last 5 years may be included but only after consultation with the Chief Investigator.
    e. Patients with celiac disease controlled by diet alone.
13. Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia QTcF value >470 ms on ECG, interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent.
14. History of another primary malignancy except for:
    - Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of IP and of low potential risk for recurrence.
    - Localized breast or prostate cancer treated with hormonal therapy alone.
    - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
    - Adequately treated carcinoma in situ without evidence of disease.
15. Leptomeningeal carcinomatosis.
16. Untreated, symptomatic central nervous system (CNS) metastases. Any neurologic symptoms that developed either as a result of the brain metastases or their treatment must have resolved or be stable either, without the use of steroids, or are stable on steroids and/or anticonvulsants prior to the start of treatment.
17. History of active primary immunodeficiency.
18. Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), hepatitis B (known positive HBV surface antigen (HBsAg) result), hepatitis C. Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
19. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab. The following are exceptions to this criterion:

- Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection).
- Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent.
- Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication).

20. Receipt of live attenuated vaccine within 30 days prior to the first dose of IP. Note: Patients, if enrolled, should not receive live vaccine whilst receiving IP and up to 30 days after the last dose of IP.
21. Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of durvalumab monotherapy.
22. Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients.
23. Judgment by the investigator that the patient is unsuitable to participate in the study and the patient is unlikely to comply with study procedures, restrictions and requirements.

Procedures for withdrawal of incorrectly enrolled patients are presented in 9.1.2.

7.3 Withdrawal of patients from study treatment and/or study

7.3.1 Permanent discontinuation of chemotherapy and durvalumab

Discontinuation of study treatment, for any reason, does not impact the patient's participation in the study. A patient who decides to discontinue IP should be asked about the reason(s) for discontinuation and the presence of any AE. The patient should continue attending subsequent study visits, and data collection should continue according to the study protocol. If the patient does not agree to continue in-person study visits, a modified follow-up must be arranged to ensure the collection of endpoints and safety information. This follow-up could be a telephone contact with the patient, a contact with a relative or treating physician, or information from medical records. The approach taken should be recorded in the medical records. A patient who agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

Patients who permanently discontinue study treatment for other reasons than objective RECIST disease progression should be followed according to the study schedule similar to patients who are on study treatment.

All patients will be followed for survival until the end of the study. Patients who decline to return to the site for evaluations should be contacted by telephone if they agree.

7.3.2 Lost to follow-up

Patients will be considered lost to follow-up only if no contact has been established by the time the study is completed, such that there is insufficient information to determine the patient's status at that time. Investigators should document attempts to re-establish contact with patients.

In order to support key end points of PFS and OS analyses, the survival status of all patients in the full analysis and the safety analysis sets should be re-checked, this includes those patients who withdrew consent or are classified as "lost to follow-up". For patients lost to follow-up, site personnel should check hospital records, the patients' current physician, and a publicly available death registry (if available) to obtain survival status.

If a patient has actively withdrawn consent to the processing of their personal data, the survival status of the patient can be obtained by site personnel from publicly available death registries (if available) where it is possible to do so under applicable local laws to obtain a current survival status.

7.3.3 Withdrawal of consent

Patients are free to withdraw from the study at any time without prejudice to further treatment. Patients who withdraw consent for further participation in the study will not receive any further study treatment or further study observation, with the exception of follow-up for survival, which will continue until the end of the study unless the patient has expressly withdrawn their consent to survival follow-up. Note that the patient may be offered additional tests or tapering of treatment to withdraw safely.

A patient who withdraws consent may be asked about the reason(s) for withdrawal and the presence of any AE but does not have to give reasons for withdrawing. The Investigator will follow up AEs outside of the clinical study. If a patient withdraws consent, they will be specifically asked if they also withdraw consent to all further follow-up (e.g. survival contact phone calls).

7.4 End of trial

Patients will be enrolled until the target number of patients who have received three or more courses of chemoimmunotherapy in the control arm and the target number of patients who have received three or more courses of chemoimmunotherapy plus TRT in the experimental arm have been reached. Recruitment will stop earlier if:

- recommended by the Data and Safety Monitoring Committee
- recruitment of patients is so slow that it is not possible to answer the research questions within a reasonable timeframe. This will be decided by Sponsor after discussion with National Coordinating Investigators.
- new data show that eligible patients should be offered other and better treatment.
- new data show that participation puts patients at unreasonable risk and/or there are no reasons to believe that the patients benefit from participating in the trial.

8. Study therapy

8.1 Durvalumab

8.1.1 Durvalumab schedule

All patients will receive 1500 mg durvalumab IV on day 1 of each chemotherapy course regardless of delays of chemotherapy courses. Durvalumab is administered before carboplatin/etoposide.

After completion of chemotherapy, they will then receive durvalumab 1500 mg IV every 4 weeks until PD and need for other treatment, unacceptable toxicity or patients wish to discontinue.

If a patient's weight falls to 30 kg or below (≤30 kg) the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg.

8.1.2 Formulation/packaging/storage

Durvalumab will be supplied by AstraZeneca as a 500-mg vial concentrate for solution for infusion. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine-hydrochloride, 275 mM trehalose dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 6.0 and density of 1.054 g/mL. The label-claim volume is 10.0 mL.

Durvalumab is a sterile, clear to opalescent, colorless to slightly yellow solution free from visible particles. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Investigational product should be kept in original packaging until use to prevent prolonged light exposure.

8.1.3 Preparation of durvalumab doses for administration with an IV bag

The dose of durvalumab for administration must be prepared by the Investigator's or site's designated IP manager using aseptic technique. Please refer to local prescribing information for in-use storage conditions and times.

A dose of 1500 mg (for patients >30 kg in weight) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 15 mg/ml and delivered through an IV administration set with a 0.2- or 0.22-µm filter. Add 30 mL (i.e. 1500 mg) of durvalumab to the IV bag. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

If a patient's weight falls to ≤ 30 kg weight-based dosing at 20 mg/kg will be administered using an IV bag size selected such that the final concentration is between 1 and 15 mg/mL.

Standard infusion time is 1 hour, however, if there are interruptions, the total infusion time must not exceed 8 hours at room temperature. Do not co-administer other drugs through the same infusion line.

The IV line will be flushed according to local practice to ensure that the full dose is administered. Infusion time does not include the final flush time.

If either preparation time or infusion time exceeds the time limits a new dose must be prepared from new vials. Durvalumab does not contain preservatives, and any unused portion must be discarded.

8.1.4 Monitoring of dose administration

Patients will be monitored before, during and after the infusion of durvalumab. Patients are monitored (pulse rate, blood pressure) every 30 minutes during the infusion period (including times where infusion rate is slowed or temporarily stopped).

In the event of a ≤Grade 2 infusion-related reaction, the infusion rate of study drug may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. For patients with a ≤Grade 2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial rate.

Acetaminophen and/or an antihistamine (e.g., diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator. If the infusion-related reaction is Grade 3 or higher in severity, study drug will be discontinued. The standard infusion time is one hour. If there are interruptions during infusion, the total allowed time from infusion start to completion of infusion should not exceed 8 hours at room temperature (otherwise a new infusion preparation is required). For management of patients who experience an infusion reaction, please refer to the toxicity and management guidelines in Appendix 1.

As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit patients to an intensive care unit if necessary.

8.2 Carboplatin and etoposide chemotherapy

8.2.1 Formulation/packaging/storage

Commercially available drugs will be used. The drugs will be stored according to label.

All patients are to receive four courses of carboplatin (area under the curve (AUC) 5 mg/ml per min, Calvert's formula) iv on day 1 plus etoposide 100 mg/m^2 BSA iv day 1 followed by etoposide 200 mg/m^2 po or etoposide 100 mg/m^2 BSA IV days 2-4. Courses are administered every 3 weeks until a maximum of four courses.

BSA is calculated according to the formula by Dubois and Dubois: BSA=0.007184 x weight$^{0.425}$ x height$^{0.725}$. It is recommended to consider capping the dose at a BSA of 2.2 m^2.

Calvert's formula: carboplatin dose (mg) = AUC (mg ml-1 min) x [GFR (ml/min) + 25 (ml/min)

For most patients, GFR/creatinine-clearance will be calculated according to the Cockroft-Gault formula. For patients with a body weight falling below 30 kg or a serum-creatinine below the lower normal value, creatinine-clearance should be measured by 24-hour urine collection.

It is recommended to reduce the etoposide-dose by 25% if creatinine-clearance is below 50 mg/minute. The use of G-CSF is allowed.

8.2.2 Product preparation and administration

According to local routines. Suggested preparation and administration of carboplatin plus etoposide:

Day 1:

- Carboplatin is diluted in 500 ml 5% glucose and infused over 30 minutes
- Etoposide is diluted in 500 ml 0.9% NaCl and infused over 30 minutes

Day 2-4:

- Half the etoposide-dose is taken orally in the morning, half the dose in the evening. The tablets are

taken with a glass of water. If etoposide is given IV, it will be administered as on Day 1.

8.2.3 Suggested antiemetic medication (carboplatin)

Day 1:

- Ondansetron 16 mg PO or IV plus dexamethason 8 mg PO or IV (or equipotent dose of other corticosteroid) 1 hour before infusion of chemotherapy commences

Day 2-3:

- Dexamethason 8 mg PO (or equipotent dose of another corticosteroid)

Other antiemetic therapy may be administered according to local routines.

8.2.4 Recommendations before a new course of chemotherapy:

- All grade 3-4 adverse events should have resolved to grade 0-2 or to the same level as before the preceding course of chemotherapy
- ANC ≥ 1.5 x 10^9/L and platelets ≥ 100 x 10^9/L. Lower values might be acceptable if the nadir-phase has passed.
- Creatinine < 125 µmol/litre (if creatinine ≥ 125 µmol/litre, cisplatin should be replaced with carboplatin)

8.2.5 Suggestions for dose adjustments:

- In case of grade 4 neutropenia (< 0.5 x 10^9/L), grade 4 thrombocytopenia (< 50 x 10^9/L) or febrile neutropenia (< 1.0 x 10^9/L, fever and treatment with antibiotics) after the preceding course, it is suggested to reduce the doses for the next course to 80% of the preceding course.
- If ANC < 1.5 x 10^9/L or platelets < 100 x 10^9/L on day 22 (day for the next course), it is suggested to delay the next course until resolution of the cytopenia. A dose reduction of 20% is suggested if a course is postponed more than a week.
- If a course is postponed more than three weeks, the chemotherapy should be discontinued.

8.2.6 Duration of treatment and criteria for treatment through progression and for retreatment

Maximum 4 courses of chemoimmunotherapy will be administered. Durvalumab treatment will then continue until PD and need for other treatment, unacceptable toxicity or patients wish to discontinue.

Chemotherapy should be discontinued if a course is postponed more than three weeks, and may be discontinued earlier if severe, unacceptable, toxicity considered to be due to the chemotherapy occurs. Patients may continue durvalumab regardless of the number of chemotherapy courses completed provided the criteria for discontinuation of durvalumab are not met.

Chemo- and/or immunotherapy will be discontinued if RECIST 1.1-defined radiological progression and need for other treatment occur. Other reasons for discontinuation include unacceptable toxicity, withdrawal of consent, or patient's wish.

During the treatment period, patients who are clinically stable at an initial RECIST 1.1-defined PD may continue to receive study treatment at the discretion of the Investigator and patient as long as they are deemed to be receiving clinical benefit. In case, a follow-up scan is to be collected after the initial RECIST 1.1-defined PD, 4-6 weeks after the prior assessment of PD for confirmation of PD and to ensure that potentially rapid progression of relapsing SCLC is revealed within a reasonable timeframe to ensure that patients may be offered other treatment for PD.

Patients with PD who continue to receive IP at the discretion of the Investigator should undergo image acquisitions and tumor assessments according to the regular schedule for the duration of treatment.

Patients with rapid tumor progression or with symptomatic progression that requires urgent medical intervention (e.g. CNS-metastasis, respiratory failure due to tumor compression, or spinal cord compression) will usually not be eligible for continuing durvalumab treatment. If a general disease control has been achieved, and oligometastatic progression occurs, exceptions may be considered after discussing with the Chief Investigator.

For all patients who are treated through progression and for patients who are restarting

durvalumab (alone or in combination with chemotherapy), the Investigator should ensure that:

- The patient does not have any significant, unacceptable, or irreversible toxicities that indicate continuing treatment will not further benefit the patient. The patient may not have experienced a toxicity that required permanent discontinuation of study treatment.
- There is absence of clinical symptoms or signs indicating clinically significant disease progression accompanied by a decline in WHO/ECOG performance status to >1
- There is absence of rapid disease progression or threat to vital organs or critical anatomical sites (e.g. CNS-metastasis, respiratory failure due to tumor compression, or spinal cord compression) requiring urgent alternative medical intervention
- The patient still fulfills the eligibility criteria for this study (see 7.1) with the exception of inclusion criteria 8, 9, 11 and 12 and exclusion criteria 3 and 8. Patients must agree to restart durvalumab therapy.
- The patient has not received an intervening systemic anticancer therapy after their assigned treatment discontinuation.
- The patient has had a retreatment baseline tumor assessment within a maximum of 28 days prior to restarting their assigned treatment; all further scans should occur with the same frequency as during the initial 12 months of treatment (relative to the date of restarting treatment) until study treatment is stopped (maximum of 12 months of further treatment).

Patients who the Investigator determine may not continue treatment after RECIST 1.1-defined PD will be followed for survival. Patients who have discontinued treatment due to toxicity or symptomatic deterioration, or who have commenced subsequent anticancer therapy, will be followed up with tumor assessments until RECIST 1.1-defined PD plus an additional follow-up scan or until death (whichever comes first) and followed for survival.

8.2.7 Accountability and dispensation

All sites will keep drug accountability records during the study. At most sites, these records will be maintained and kept at the local pharmacy.

8.2.8 Disposition of unused investigational study drug

The site will account for all investigational study drug dispensed and appropriately destroyed. Certificates of delivery and destruction must be signed and reported to sponsor.

8.2.9 Monitoring of dose administration

According to local routines.

8.3 Thoracic radiotherapy

8.3.1 Timing

Ideally, patients randomized to the experimental arm are to receive TRT between the second and third chemo-immunotherapy course. TRT may start concurrently with the second course, and TRT should be completed before the third chemo-immunotherapy course commences.

However, there might be logistical challenges if chemo-immunotherapy courses are delayed due to toxicity from chemo-immunotherapy. In case, TRT may start after the second course even if the second course is delayed, but TRT may also start as scheduled regardless of the delay of the second chemo-immunotherapy course (i.e. 21-28 days after the first day of the first chemo-immunotherapy).

If TRT is delayed due to intercurrent disease prohibiting TRT starting as planned, TRT should be administered as soon as possible. If TRT is not administered, patients should still receive chemo-immunotherapy as scheduled.

8.3.2 TRT fractionation schedule

Patients should receive 30 Gy in 10 fractions, 5 fractions per week. The optimal treatment time is 12 days,

but up to 15 days is allowed in case of holidays or unplanned delays.

8.3.3 Treatment planning CT-scan

The treatment planning CT scan (or PET CT scan if that is the local routine) should be done with the patient immobilized in supine position according to local standard procedures for radiotherapy of the thorax. The whole thorax should be included in the CT scan and IV contrast should be used. Slice thickness should be ≤ 3 mm. The use of 4DCT is recommended and breath-hold technique or gating is allowed, but not mandatory.

8.3.4 TRT guidelines in the CREST trial

The planning target volume (PTV) was defined as the post-chemotherapy volume with a margin of 15 mm. The initially positive hilar and mediastinal nodal stations were included, also in case of a complete response. The V_{20} should be <35% of the total lung volume. A lung correction was required for all treatment plans. All modern RT techniques (including IMRT and VMAT) were allowed. The definition of volumes and calculation of doses should be performed according to the ICRU.[48]

8.3.5 Targets for TRT in the present trial

Preferably, the target volume should include the primary lung tumor and regional lymph node metastases identified before chemoimmunotherapy commenced, also in case of a complete response. Extensive, elective nodal irradiation is not allowed.

If possible, all thoracic lesions should be included in the radiotherapy field. If this is not possible, lesions compressing central airways or mediastinal structures (e.g. large vessels and nerves) should be prioritized. A minimum of one lesion should be irradiated. If a complete response is achieved by the time of the CT planning scan, this lesion may be a previously enlarged lymph node.

8.3.6 Delineation of target volumes

The gross tumor volume (GTV) will include the residual volume after the first (or second) chemoimmunotherapy course. The clinical target volume (CTV) will account for microscopic spread and is generated by expanding the GTV with 5 mm in all directions, but not across anatomic barriers such as trachea, heart, esophagus, bones, except when there is radiological invasion into these structures. The planning target volume (PTV) is defined by expanding the CTV with a margin defined according to local routines.

8.3.7 Delineation of organs at risk (OARs) and corresponding normal tissue dose constraints

In thoracic radiation the critical normal structures (organs at risk) that are likely to receive a significant radiation dose are: spinal cord; lungs; heart and pericardium; oesophagus. It is important to know the dose delivered to these structures, as this must be kept within normal tissue 'tolerance'. The following OARs should be contoured:

Organ at risk	Physical dose	Delineation
Lungs	Mean lung dose ≤12 Gy $V_{20\,Gy}$ <30% $V_{5\,Gy}$ preferably <55%	Both lungs minus GTV (IGTV)
Spinal canal	$D_{0.03\,cm3}$ ≤ 30 Gy	Contoured as the bony edge of the vertebral foramens from 2 cm above and below the PTV
Heart	$V_{10\,Gy}$ <10% Mean heart dose should be as low as possible	The whole heart below the division of the truncus pulmonalis
Esophagus	$D_{0.03\,cm3}$ ≤ 30 Gy Mean esophageal dose should be as low as	From just below the larynx to the gastric-esophageal junction

	possible. Hot spots in the esophagus should be avoided.	

8.3.8 Treatment planning

Megavoltage equipment with a nominal photon energy of 6 MV is recommended. Inverse planning techniques like intensity modulated RT (IMRT) and rotational techniques such as volumetric modulated arc therapy (VMAT) and modern dose calculation algorithms (Monte Carlo, AAA, Collapsed Cone etc) should be used. A dose calculation grid of 2 mm^3 is recommended. A median dose of 30 Gy should be delivered to the CTV. 98% of the PTV should be covered by the 95 % isodose. In those parts of the PTV consisting of normal lung tissue, a coverage of the 90% isodose is sufficient. A near maximum dose ($D_{2\%}$) of 107% is accepted.

8.3.9 Treatment

Daily cone beam CT (CBCT) with soft tissue match according to the target volume is mandatory.

8.3.10 Quality assurance of the thoracic radiotherapy

The first radiotherapy plan at each site should be sent to the central trial office in Trondheim as soon as possible. All radiotherapy plans will be reviewed by a study physician and a medical physicist, and feedback provided within 5 working days. When all patients have completed TRT, all radiotherapy plans should be sent to the central trial office for review.

8.3.11 TRT in the control arm

TRT may be offered patients in the control arm upon progression if this is considered the best alternative. Routine consolidation TRT after completion of chemoimmunotherapy is not allowed.

8.4 Prophylactic cranial irradiation (PCI)

PCI is not mandatory, but patients who respond to chemoimmunotherapy and have not previously received brain irradiation, should be offered PCI at the hospitals where this is established treatment of ES SCLC.

PCI should start between 4 to 6 weeks after the last chemoimmunotherapy course. PCI should be administered according to local routines. Hippocampus-sparing PCI is allowed. Recommended schedules are 25 Gy in 10 fractions or 30 Gy in 15 fractions. One schedule should be used for all patients at each site. PCI may be administered concurrently with durvalumab infusions.

8.4.1 Treatment of brain metastases

The treatment of brain metastases varies between hospitals. Patients with brain metastases may receive whole brain radiotherapy (WBRT) before or after chemoimmunotherapy. Recommended schedules are 30 Gy in 10 fractions (preferred) or 20 Gy in 4-5 fractions. WBRT should be administered according to local routines. WBRT may be offered patients who have received PCI if this is the local treatment policy.

An alternative to WBRT is stereotactic radiosurgery (SRS) provided the number, size and location of the brain metastases allows for SRS. The role of SRS in brain metastases from SCLC is less defined than for NSCLC, but especially for patients who have received PCI, have good and long extracranial disease control, and limited number of brain metastases, SRS may be a better alternative than WBRT. Surgery may be an alternative but is seldom offered SCLC patients.

Isolated progression in the brain does not necessarily warrant a change in systemic treatment provided local control is achieved by SRS, WBRT or surgery.

8.4.2 Irradiation of other lesions

Irradiation of other lesions is allowed according to each hospital's routines. This applies for both trial arms. If possible, it is preferred that any additional RT in the control arm is delivered after completion of chemo-immunotherapy.

8.5 Post study therapy

Upon progression, patients should be treated according to each hospital's routines. All post-study treatment, including all RT, should be recorded.

9. Treatment plan

9.1 Patient enrollment and randomization

9.1.1 Procedures for randomization

After patients are assigned a study ID and registered in the CRF, investigators randomize patients using the randomization module in the CRF. Patients will be randomized 1:1 in blocks of various sizes to receive chemo-immunotherapy alone or chemo-immunotherapy plus TRT stratifying for presence of liver metastases (yes vs. no), and presence of brain metastases (yes vs. no). The study is open label, and patients and investigators will know the results of the randomization. They will not, however, know the results of previous randomizations or the block sizes.

9.1.2 Procedures for handling patients incorrectly enrolled

Patients who are incorrectly enrolled and/or randomized will be discussed with the Chief Investigator before deciding whether the patient should be withdrawn. If there has been a major protocol violation, the patient will be withdrawn from the study.

10. Restrictions during the study and concomitant treatment(s)

10.1 Restrictions during the study

The following restrictions apply while the patient is receiving study treatment and for the specified times before and after:

Female patient of child-bearing potential:

- Female patients of childbearing potential who are not abstinent and intend to be sexually active with a non-sterilized male partner must use at least 1 highly effective method of contraception (Table 1) from the time of screening throughout the total duration of the drug treatment and the drug washout period (90 days after the last dose of durvalumab monotherapy). Non-sterilized male partners of a female patient of childbearing potential must use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Female patients should also refrain from breastfeeding throughout this period.

Male patients with a female partner of childbearing potential:

- Non-sterilized male patients who are not abstinent and intend to be sexually active with a female partner of childbearing potential must use a male condom plus spermicide from the time of screening throughout the total duration of the drug treatment and the drug washout period (90 days after the last dose of durvalumab monotherapy). Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male patients should refrain from sperm donation throughout this period.
- Female partners (of childbearing potential) of male patients must also use a highly effective method of contraception throughout this period (Table 1).

N.B Females of childbearing potential are defined as those who are not surgically sterile (i.e. bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) or post-menopausal.

Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

- Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing

hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution.

- Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago.

Highly effective methods of contraception, defined as one that results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly are described in Table 1. Note that some contraception methods are not considered highly effective (e.g. male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).

Table 1 Highly Effective Methods of Contraception (<1% Failure Rate)

• Barrier/Intrauterine methods	• Hormonal Methods
• Copper T intrauterine device • Levonorgestrel-releasing intrauterine system (e.g., Mirena®)[a]	• Implants: Etonogestrel-releasing implants: e.g. Implanon® or Norplant® • Intravaginal: Ethinylestradiol/etonogestrel-releasing intravaginal devices: e.g. NuvaRing® • Injection: Medroxyprogesterone injection: e.g. Depo-Provera® • Combined Pill: Normal and low dose combined oral contraceptive pill • Patch: Norelgestromin/ethinylestradiol-releasing transdermal system: e.g. Ortho Evra® • Minipill: Progesterone based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone-based

[a] This is also considered a hormonal method

10.1.1 Blood donation

Patients should not donate blood while participating in this study, or for at least 90 days following the last infusion of durvalumab or 90 days after receipt of the final dose of durvalumab.

10.2 Concomitant treatment(s)

10.2.1 Permitted concomitant medications

Table 2 Supportive Medications

Supportive medication/class of drug:	**Usage:**
Concomitant medications or treatments (e.g., acetaminophen or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited," as listed above	To be administered as prescribed by the Investigator
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative RT to non-target lesions])	Should be used, when necessary, for all patients
Inactivated viruses, such as those in the influenza vaccine	Permitted

10.2.2 Excluded concomitant medications

Table 3 Prohibited Concomitant Medications

Prohibited medication/class of drug:	Usage:
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
Any concurrent chemotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment. (Concurrent use of hormones for non-cancer-related conditions [e.g., insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [e.g., by local surgery or RT])
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers	Should not be given concomitantly or used for premedication prior to the I-O infusions. The following are allowed exceptions: • Use of immunosuppressive medications for the management of IP-related AEs • Short-term antiemetic therapy in relation with chemotherapy-courses • For the treatment of hypersensitivity reactions caused by the study treatment • Use in patients with contrast allergy • Use of inhaled, topical and intranasal corticosteroids is permitted A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy related events experienced by the patient (e.g., chronic obstructive pulmonary disease, radiation, nausea, etc.).
Live attenuated vaccines	Should not be given through 30 days after the last dose of IP (including SoC)
Herbal and natural remedies which may have immune-modulating effects	Should not be given concomitantly unless agreed by the sponsor

11. Study procedures

11.1 Schedule of study procedures

Before study entry, throughout the study, and following study drug discontinuation, various clinical and diagnostic laboratory evaluations are outlined. The purpose of obtaining these detailed measurements is to ensure adequate safety and tolerability assessments. Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated.

11.1.1 For both treatment arms

- An early response evaluation will be performed 3-4 weeks after the first chemo-immunotherapy course (at the time of TRT start in the experimental arm). For patients randomized to the experimental arm, the CT planning scan might be used for response evaluation. For patients on the control arm, a regular CT scan must be performed.
- Response evaluation and measurement of HRQoL after completion of chemo-immunotherapy will be

performed 2-3 weeks after the fourth course

- If chemotherapy is discontinued before the fourth course, response evaluation and HRQoL measurement will be performed according to schedule (week 11-12).
- Subsequent tumor efficacy (RECIST) and other assessment dates are not affected by dose delays and remain as originally scheduled, as they are based on the date of inclusion and not the date of therapy.

11.1.2 For durvalumab maintenance therapy

- Patients may delay dosing under certain circumstances such as e.g. intercurrent disease and holidays if this is considered appropriate by their physician.
- Dosing may be delayed per Toxicity Management Guidelines, due to either an immune or a non-immune-related AE.
- If dosing must be delayed for reasons other than treatment-related toxicity, dosing will resume as soon as feasible
- Dosing intervals of subsequent cycles may be shortened as clinically feasible in order to gradually align treatment cycles with the schedule of tumor efficacy (RECIST) and patient reported outcomes (PRO) assessments. Subsequent time between 2 consecutive doses cannot be less than 22 days, based on the half-lives of durvalumab (see current Investigator Brochure for durvalumab).

11.1.3 Screening phase

Screening procedures will be performed up to 28 days before Day 1 of the first chemo-immunotherapy course, unless otherwise specified. All patients must first read, understand, and sign the IRB/REB/IEC-approved ICF before any study-specific screening procedures are performed. After signing the ICF, completing all screening procedures, and being deemed eligible for entry, patients will be enrolled in the study. Procedures that are performed prior to the signing of the ICF and are considered standard of care may be used as screening assessments if they fall within the 28-day screening window.

The following procedures will be performed during the screening visit:

- Informed Consent
- Review of eligibility criteria
- Medical history, demographics, and smoking history
- Complete physical exam
- ECOG Performance Status
- Weight and height
- 12-lead ECG (in triplicate if there are any significant abnormalities on the first ECG, each recording should be made 2-5 minutes apart)
- Review of prior/concomitant medications
- CT of the thorax and upper abdomen
- MRI of the brain
- Pulmonary function
- Cognitive function (MoCA test)
- HRQoL-questionnaire
- Pregnancy test in women of childbearing potential
- Collection of blood and stool samples for biomarker analyses including neuronal auto-antibodies
- Clinical laboratory tests for:
  - Hematology (see Table 4)
  - Clinical chemistry (see Table 5)
  - Creatinine Clearance
  - Serum pregnancy test (for women of childbearing potential only)

- Hepatitis serologies

11.1.4 Treatment phase

Procedures to be conducted during the treatment phase of the study are presented in the SoAs. Screening procedures performed within 5 days of Day 1 of the first chemoimmunotherapy course do not need to be repeated before study treatment commences.

11.1.5 End of treatment

Assessments for patients who have completed durvalumab treatment and achieved disease control or have discontinued durvalumab due to toxicity in the absence of confirmed progressive disease, and for those who have progressed are provided below the schedule of events on page 11.

All patients will be followed for survival until the end of the study regardless of further treatments, or until the sponsor ends the study.

11.2 Patient reported outcomes (PRO)

11.2.1 Assessment of health-related quality of life (HRQoL)

HRQoL will be assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) C30 and the lung cancer specific module LC13. The QLQ-C30 measures fundamental aspects of HRQoL and symptoms commonly reported by cancer patients in general, the LC13 measures symptoms commonly associated with lung cancer and its treatment.[61,62]

Patients will complete the questionnaires on paper. The questionnaires are either handed patients by local study personnel or mailed them from the central trial office in Trondheim. Patients will return the completed questionnaires in enclosed, prepaid envelopes provided by the central trial office. If patients who receive the questionnaires via mail do not return a completed questionnaire within 14 days, a reminder will be mailed.

When questionnaires are handed to patients by local study personnel, the study personnel will check that the questionnaire is completed correctly before they are stored locally. All questionnaires are mailed to the central trial office by completion of the trial or upon request from the trial office. If the questionnaires may not be mailed to the central trial office due to local laws or regulations, the local study personnel will enter the responses in the CRF.

11.3 Assessment of cognitive function

Cognitive function will be assessed using the Montreal Cognitive Assessment (MoCA).[63] The assessment will be performed by trained study personnel. The training is performed online at mocatest.org. Study personnel will enter the results in the CRF.

11.4 Biological sampling procedures

11.4.1 Collection of biological material for translational research

We will collect tumor samples, blood samples (whole blood, plasma, serum) and stool for biomarker analyses.

11.4.2 Tissue samples

We will collect diagnostic tissue samples and biopsies collected at relapse when possible to collect. We will collect formalin-fixed, paraffin-embedded and not fresh frozen tissue.

It is recommended that tissue samples are placed immediately (within 30 min of excision) into an adequate volume of 10% v/v neutral buffered formalin (NBF). Samples should remain in fixative for 24 – 48 hours at room temperature. It is vital that there is an adequate volume of fixative relevant to the tissue (at least a 10-volume excess) and that large specimens (if any) are incised prior to fixation to promote efficient tissue preservation.

An overnight processing schedule into paraffin wax is recommended, and FFPE blocks should be stored at ambient temperature and protected from light until shipment by courier at ambient temperature. FFPE blocks are stable under these conditions for an indefinite period.

The samples are to be shipped to the central trial office in Trondheim when enrollment of patients has

been completed or upon request.

Blocks of formalin-fixed, paraffin-embedded tissue is preferred, but slides are also welcome. Slides should be cut immediately before shipping, and the time point for shipping will be agreed upon with each site. Details on how to cut slides will be provided when shipping of blocks or slides is requested.

11.4.3 Blood samples

The following blood samples for biomarker analyses will be collected:

Serum

- 18 ml blood should be collected in 3 x 6 ml serum tubes (e.g. Vacuette Z serum clot activator tubes or similar) for isolation of serum.
- The tubes should be turned gently 8-10 times and left in a standing position at room temperature for 30-60 minutes.
- Centrifuge the tubes at 2500 g at room temperature for 10 minutes.
- After centrifugation, the serum should be aliquoted into 4 cryotubes, 1.5 ml in each. If more serum is available, increase the aliquots to 1.8 ml.
- All tubes should be labeled and stored at -80°C until shipment.

Plasma

- 30 ml blood should be collected in 5 x 6 ml EDTA tubes for isolation of plasma.
- The tubes should be turned gently 8-10 times to dissolve the anticoagulant.
- Centrifuge the tubes as soon as possible and within 60 minutes in a horizontal rotor (both swing-out and fixed rotors are ok) at 1600 g at 4°C for 15 minutes.
- After centrifugation, the plasma layer will be at the top of the tube. Mononuclear cells and platelets will be in a whitish layer, called the “buffy coat”, below the plasma and above the red blood cells.
- Carefully collect the plasma with a sterile pipette (in a sterile hood) without disturbing the buffy coat layer and transfer the plasma to Eppendorf tubes.
- Centrifuge the Eppendorf tubes at 10 000 g at 4°C for 10 minutes, then transfer plasma into 4 x 4.5 ml cryotubes, up to 4 mL in each.
- Collect the buffy coat from all tubes and transfer to two cryotubes.
- All tubes should be labeled and stored at -80°C until shipment.

EDTA whole blood (only at inclusion)

- 6 ml blood should be collected in one EDTA tube for genetic analysis.
- The tube should be turned gently 8-10 times to dissolve the anticoagulant and aliquoted into 4 x 1.8 ml cryotubes with a minimum of 1 ml in each.
- All tubes should be labeled and stored at -80°C until shipment.

PAX tube

- 2.5 ml blood should be collected in one 10 ml PAX-tube.
- The tube should be turned gently 8-10 times and left in a standing position in room temperature for 2-3 hours before placed in freezer at -20°C for 24 hours. Do not store tubes in Styrofoam trays, as it could cause the tubes to crack.
- Transfer the tube to -80°C after 24 hours.
- All tubes should be labeled and stored at -80°C until shipment.

We are aware that not all sites have access to centrifuges with the descried capacity. The impact of centrifuge speed on the material quality is undetermined, and we will collect samples regardless of equipment. All sites will report the capacity of the centrifuges used for processing of blood samples. Labels for the tubes will be supplied from the central trial office in Trondheim.

11.4.4 Stool samples

Patients will be handed a kit for stool sampling including instructions for sampling. Patients will apply a sample on an appropriate medium and deliver at the study site in an envelope designed for this purpose. The stool samples should be labeled and stored at -80°C until shipment. Labels will be supplied from the central trial office in Trondheim. Details on stool sampling will be provided in the study procedure manual.

11.4.5 Proposed biomarker analyses

There are no established predictive markers for effect of ICI, chemotherapy or RT in SCLC. PD-L1 and TMB, the most relevant predictive markers in other types of cancer, do not appear to be clinically relevant in SCLC.

A molecular classification of SCLC based on RNA-sequencing has been proposed,[64] and there are indications that such classification might be used to predict treatment response.[65] Recently, a study found that germline genotype was associated with recurrence-free survival after platinum chemotherapy.[66] Thus, we will investigate the prognostic and predictive role of these molecular profiles in this trial.

Few have investigated the clinical role of ctDNA in SCLC, but data from NSCLC studies suggest that changes in ctDNA occur before response to immunotherapy can be evaluated on CT scans.[67] Thus, we will investigate the prognostic value of baseline ctDNA analyses (presence of detectable mutations and quantification), and associations between dynamics of known SCLC-related mutations in ctDNA are associated with response to therapy and treatment outcomes, especially long-term survival.

miRNA-profile is a highly relevant marker associated with extent of disease, tumor biology and prognosis.[68] Few have investigated whether this is the case in SCLC. We will investigate associations between miRNA profile and the outcomes as described above - both for miRNA alone, and as part of an integrative model including both sequencing data from tissue, ctDNA and miRNA-analyses.

There are strong indications of associations between gut microbiome and response to ICI,[69,70] but this is scarcely investigated in SCLC. We assess the microbiome through sequencing, and investigate whether there are associations with the tumor, ctDNA or miRNA-profile - or treatment outcomes. To facilitate a correct interpretation, we will collect information about concomitant medication and use of antibiotics the last 6 months before study enrolment from all patients, since antibiotics are known to influence the gut microbiome.

We plan to start the biomarker analyses one year after enrolment in the trial has been completed. There is a lot of ongoing research on prognostic and predictive factors in patients who receive ICI, and based on research results published until then, other markers may be added to the analyses plan. A final plan describing analyses and techniques will be defined when enrolment is close to complete.

11.4.6 Withdrawal of informed consent for donated biological samples

If a patient withdraws, collection of data and biological material will stop, but according to Norwegian legislation, already collected data and material will be included in the analyses.

12. Disease evaluation and methods

The response to immunotherapy may differ from the typical responses observed with cytotoxic chemotherapy including the following (Wolchok et al 2009, Nishino et al 2013):

- Response to immunotherapy may be delayed
- Response to immunotherapy may occur after PD by conventional criteria
- The appearance of new lesions may not represent PD with immunotherapy
- SD while on immunotherapy may be durable and represent clinical benefit.

Based on the above-described unique response to immunotherapy and based on guidelines from regulatory agencies, e.g., European Medicines Agency's "Guideline on the evaluation of anticancer medicinal products in man" (EMA/CHMP/205/95/Rev.4) for immune modulating anticancer compounds, the study implements the following in addition to standard RECIST 1.1 criteria:

- PD must be confirmed after 4-6 weeks if study treatment continues beyond PD. If clinically significant deterioration occurs, a new CT scan should be performed earlier to ensure that patients are offered relapse treatment at a time when they still may benefit from other therapies.
- Patients may continue to receive durvalumab beyond confirmed PD in the absence of clinically significant deterioration and if investigators consider that patients continue to receive benefit from treatment.

Modification of RECIST as described may discourage the early discontinuation of durvalumab and provide a more complete evaluation of its antitumor activity than would be seen with conventional response criteria. Nonetheless, the efficacy analysis will be conducted based on the RECIST 1.1 criteria.

Of note, clinically significant deterioration which is not due to another known condition or intercurrent disease is considered to reflect a rapid tumor progression that necessitates treatment with anticancer therapy other than durvalumab or with symptomatic progression that requires urgent medical intervention (e.g. CNS metastasis, respiratory failure due to tumor compression, spinal cord compression).

12.1 Sensitivity analyses

One reason TRT is debated in ES SCLC, is that it may be problematic to offer palliative TRT for local relapse if patients receive TRT as part of their primary therapy. Thus, assessing the local relapse rate and time to local relapse is of great interest in this trial, since the survival benefit of TRT alone is limited, and that adding immunotherapy to chemotherapy may prolong local control. Another clinical setting of great interest is the timing and number of brain metastases. There are different policies with respect of timing of brain irradiation for brain metastases and the benefit of PCI in ES SCLC is debated.

Per RECIST 1.1 definition, irradiated lesions are not considered measurable. However, for this trial, we will perform sensitivity analyses including irradiated lesions for assessment of progression since these analyses will provide important information on how to care for ES SCLC patients. In these sensitivity analyses, irradiated lesions will be classified and measured similar to non-irradiated lesions according to RECIST 1.1.

13. Assessment of safety

13.1 Clinical laboratory tests

Blood samples for determination of clinical chemistry and hematology will be taken at the times indicated in the SoAs and as clinically indicated.

Clinical laboratory safety tests, including serum pregnancy tests, will be performed in a licensed clinical laboratory according to local standard procedures. Sample tubes and sample sizes may vary depending on the laboratory method used and routine practice at the site. Pregnancy tests may be performed at the site using a licensed test (urine or serum pregnancy test). Abnormal clinically significant laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

The laboratory variables to be measured are:

Table 4 Hematology laboratory tests

Absolute neutrophile count	Hemoglobine	Leukocytes	Platelet count

Table 5 Clinical chemistry (serum or plasma) laboratory tests

Bilirubin	Aspartate aminotransferase (AST)	Alanine aminotransferase (ALT)
Alkaline phosphatase (ALP)	Creatinine	Sodium (Na)
Potassium (K)	Thyroid stimulating hormone (TSH)	Free thyroxine (FT4)
Erythrocyte sedimentation rate	Glucose	Lactate dehydrogenase (LDH)

Tri-iodothyronine (T3) if abnormal thyroid function is suspected and FT4 is normal.

Other safety tests to be performed at screening include assessment for hepatitis B surface antigen (HBsAg), hepatitis C antibodies (HCV Ab), and HIV antibodies.

If a patient shows an AST or ALT ≥3xULN together with total bilirubin ≥2xULN, refer to Section 13.15.2 for further instructions on cases of increases in liver biochemistry and evaluation of Hy's Law. These cases should be reported as SAEs if, after evaluation, they meet the criteria for a Hy's law case or if any of the individual liver test parameters fulfill any of the SAE criteria.

All patients should have further chemistry profiles performed at 30 days after permanent discontinuation of IP if the reason is an AE.

All patients with Grade 3 or 4 laboratory values at the time of completion or discontinuation from IP must have further tests performed until the laboratory values have returned to Grade 1 or 2, unless these values are not likely to improve because of the underlying disease.

13.1.1 Physical examinations

Physical examinations will be performed according to the assessment schedules (see the SoAs). Full physical examinations will include assessments of the head, eyes, ears, nose, and throat and the respiratory, cardiovascular, gastrointestinal, urogenital, musculoskeletal, neurological, dermatological, hematologic/lymphatic, and endocrine systems. Height will be measured at screening only. Targeted physical examinations are to be utilized by the Investigator on the basis of clinical observations and symptomatology. Situations in which physical examination results should be reported as AEs are described in Section 13.4.1.

Resting 12-lead ECGs will be recorded at screening and as clinically indicated throughout the study. ECGs should be obtained after the patient has been in a supine position for 5 minutes and recorded while the patient remains in that position.

At screening, a single ECG will be obtained on which QTcF must be <470 ms. In case of clinically significant ECG abnormalities, including a QTcF value >470 ms, 2 additional 12-lead ECGs should be obtained over a brief period (eg, 30 minutes) to confirm the finding before a patient in deemed ineligible.

First infusion

BP and pulse should be monitored:
- Prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes [i.e., the beginning of the infusion])
- Approximately 30 minutes during the infusion (halfway through infusion)
- At the end of the infusion (approximately 60 minutes ±5 minutes)
- If the infusion takes longer than 60 minutes, then BP and pulse measurements should follow the principles as described above or be taken more frequently if clinically indicated.

A 1-hour observation period is recommended after the first infusion of durvalumab.

Subsequent infusions

Patients should be carefully monitored with respect to BP and other vital signs prior to, during and post infusion as per institution standard and as clinically indicated.

13.2 WHO/ECOG performance status

ECOG performance status will be assessed at the times specified in the SoAs based on the following:

0 Fully active; able to carry out all usual activities without restrictions
1 Restricted in strenuous activity, but ambulatory and able to carry out light work or work of a sedentary nature (e.g., light housework or office work)
2 Ambulatory and capable of self-care, but unable to carry out any work activities; up and about more than 50% of waking hours.
3 Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4 Completely disabled; unable to carry out any self-care and totally confined to bed or chair

5 Dead

13.3 Other safety assessments

If new or worsening pulmonary symptoms (e.g., dyspnea) or radiological abnormality suggestive of pneumonitis/ILD is observed, toxicity management as described in detail in the Toxicity Management Guidelines (see Appendix 1) will be applied. It is strongly recommended to perform a full diagnostic workup (including high-resolution computed tomography [HRCT], blood and sputum culture, hematological parameters, etc.), to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of pneumonitis/ILD should be considered and the Dosing Modification and Toxicity Management Guidelines should be followed.

The Principal Investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section.

13.4 Safety parameters

13.4.1 Definition of adverse events (AEs)

The International Conference on Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline for Good Clinical Practice (GCP) E6(R2) defines an AE as:

Any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE includes but is not limited to any clinically significant worsening of a patient's pre-existing condition. An abnormal laboratory finding (including ECG finding) that requires an action or intervention by the investigator, or a finding judged by the investigator to represent a change beyond the range of normal physiologic fluctuation, should be reported as an AE.

AEs may be treatment emergent (i.e., occurring after initial receipt of investigational product) or nontreatment emergent. A non-treatment-emergent AE is any new sign or symptom, disease, or other untoward medical event that begins after written informed consent has been obtained but before the patient has received investigational product.

Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the patient being enrolled into the study) for a documented pre-existing condition, that did not worsen from baseline, is not considered an AE (serious or nonserious). An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE. The term AE is used to include both serious and non-serious AEs.

13.4.2 Definition of serious adverse events (SAEs)

An SAE is an AE occurring during any study phase (i.e., screening, run-in, treatment, wash-out, follow-up), at any dose of the study drugs that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect in offspring of the patient
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or

at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations, or development of drug dependency or drug abuse.

The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the investigator(s) and immediately reported to the central trial office on the SAE form (i.e. no more than 24 hours after learning of the event) by emailing the completed SAE-form to triplex@stolav.no.

Exception An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study treatment administration or performance of an efficacy measurement for the study) or to perform study procedures
- Hospitalization for pre-existing conditions, provided that the hospitalization was planned prior to the study and the patient has not experienced an adverse event
- Hospitalization due solely to progression or suspicion of progression of the underlying cancer

13.4.3 Definition of adverse events of special interest (AESI)

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of durvalumab and may require close monitoring. An AESI may be serious or non-serious. If the Investigator has any questions regarding an event being an immune-mediated AE (imAE), the investigator should promptly contact the Chief Investigator.

AESIs observed with durvalumab include:

- Diarrhea / Colitis and intestinal perforation
- Pneumonitis / ILD
- Hepatitis / transaminase increases
- Endocrinopathies (i.e. events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypothyroidism and type I diabetes mellitus)
- Rash / Dermatitis
- Nephritis / Blood creatinine increases
- Pancreatitis / serum lipase and amylase increases
- Myocarditis
- Myositis / Polymyositis
- Neuropathy / neuromuscular toxicity (e.g. Guillain-Barré, and myasthenia gravis)
- Intestinal Perforations

Other inflammatory responses that are rare/less frequent with a potential immune-mediated etiology include, but are not limited to:

- Pericarditis
- Sarcoidosis
- Uveitis
- Other events involving the eye and skin
- Hematological events
- Rheumatological events
- Vasculitis
- Non-infectious meningitis
- Non-infectious encephalitis

It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs.

In addition, infusion-related reactions and hypersensitivity/anaphylactic reactions with a different underlying pharmacological etiology are also considered AESIs.

Further information on these risks (e.g. presenting symptoms) can be found in the current version of the durvalumab Investigator's Brochure. More specific guidelines for their evaluation and treatment are

described in detail in the Dosing Modification and Toxicity Management Guidelines (please see Appendix 1). These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to the study drug/study regimen by the reporting investigator.

13.4.4 Pneumonitis/ILD investigation

The following assessments, and additional assessments if required, will be performed to enhance the investigation and diagnosis of potential cases of pneumonitis.

- Physical examination: Signs and symptoms (cough, shortness of breath and pyrexia, etc.) including auscultation for lung field will be assessed.
- SpO2Saturation of peripheral oxygen (SpO2)
- When pneumonitis/ILD is suspected during study treatment, the following markers should be measured where possible: ILD Markers (KL-6, SP-D) and β-D-glucan
- Tumor markers: Particular tumor markers which are related to disease progression.
- Additional Clinical chemistry: CRP, LDH

13.5 Assessment of safety parameters

13.5.1 Assessment of severity

Assessment of severity is one of the responsibilities of the investigator in the evaluation of AEs and SAEs. Severity will be graded according to the NCI CTCAE v5.0. The determination of severity for all other events not listed in the CTCAE should be made by the investigator based upon medical judgment and the severity categories of Grade 1 to 5 as defined below.

Grade 1 (mild)	An event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Grade 2 (moderate)	An event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the patient.
Grade 3 (severe)	An event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the patient.
Grade 4 (life-threatening)	An event, and/or its immediate sequelae, that is associated with an imminent risk of death or with physical or mental disabilities that affect or limit the ability of the patient to perform activities of daily living (eating, ambulation, toileting, etc.).
Grade 5 (fatal)	Death (loss of life) as a result of an event.

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 13.4.1. A Grade 3 AE need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a nonserious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

13.6 Recording of adverse events and serious adverse events

AEs and SAEs will be collected from the time of the patient signing the ICF until the follow-up period is completed or 90 days after the last dose of study treatment. If an event that starts later is considered to be a late onset toxicity to study treatment, it should still be reported as an AE or SAE.

During study participation, all AEs and SAEs should be proactively followed up for each patient for

as long as the event is ongoing. Every effort should be made to obtain a resolution for all events, even if the events continue after the patient has discontinued study treatment or the study has completed.

Any AEs that are unresolved at the patient's last visit in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the CRF.

AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

The following variables will be collected for each AE:

- Type of event/description of AE
- Maximum CTCAE grade

In addition, the following variables will be collected for SAEs as applicable:

- Description of SAE
- Date the AE met criterion for SAE
- Seriousness criteria fulfilled
- Date of hospitalization
- Date of discharge
- The date when the AE started and stopped
- The maximum CTCAE grade reported
- Investigator causality rating against the study treatment or procedure, or concomitant medication
- Action taken with regard to study treatment
- Administration of treatment for the AE
- Outcome
- Probable cause of death
- Date of death
- Whether an autopsy was performed

The grading scales found in the NCI CTCAE version 5.0 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE version 5.0 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

13.6.1 Study recording period and follow-up for adverse events and serious adverse events

If a patient discontinues from treatment for reasons other than disease progression, and therefore continues to have tumor assessments, SAEs related to study treatment of procedures must be captured until the patient is considered to have confirmed PD and will have no further tumor assessments.
The investigator is responsible for following all SAEs until resolution, until the patient returns to baseline status, or until the condition has stabilized with the expectation that it will remain chronic, even if this extends beyond study participation.

13.7 Relationship to protocol procedures

The Investigator is also required to provide an assessment of the relationship of SAEs to protocol procedures on the SAE report form. This includes both non-treatment–emergent (i.e., SAEs that occur prior to the administration of IP) and treatment-emergent SAEs. A protocol-related SAE may occur as a result of a procedure or intervention required during the study (e.g., blood collection). The following guidelines should be used by Investigators to assess the relationship of SAEs to the protocol:

- Protocol related: The event occurred due to a procedure or intervention that was described in the protocol for which there is no alternative etiology according to the patient's medical record.
- Not protocol related: The event is related to an etiology other than the procedure or intervention that was described in the protocol. The alternative etiology must be documented in the study patient's medical record.

13.8 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: “Have you had any health problems since the previous visit/you were last asked?” or revealed by observation will be collected and recorded in the CRF.
When collecting AEs, the recording of diagnoses is preferred, when possible, to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

13.9 Adverse events based on examinations and tests

The results from protocol-mandated laboratory tests and vital signs measurements will be recorded in the CRF. Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs should therefore only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of study treatment.

If deterioration in a laboratory value or vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result or vital sign will be considered as additional information. Whenever possible, the reporting Investigator should use the clinical rather than the laboratory term (e.g., anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AEs.

Deterioration of a laboratory value that is unequivocally due to disease progression should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

13.10 Disease progression

Disease progression can be considered as a worsening of a patient’s condition attributable to the disease which is being studied. It may be an increase in the severity of the disease under study and/or increase in the symptoms of the disease. The development of new or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE/SAE. Events that are unequivocally due to disease progression should not be reported as an AE/SAE during the study.

13.11 New cancers

The development of a new cancer should be regarded as an SAE. New primary cancers are other cancers than SCLC that have been identified after the patient’s inclusion in this study.

13.12 Deaths

All deaths that occur during the study treatment period, or within the protocol-defined follow-up period after the administration of the last dose of study drug, must be reported as follows:

- Death clearly resulting from disease progression should be reported to the Study Monitor/Physician at the next monitoring visit and should be recorded in the CRF. It should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the Study Monitor/Physician as an SAE within 24 hours. It should also be recorded in the CRF.
- The report should contain a comment regarding the co-involvement of PD, if appropriate, and should assign main and contributory causes of death.
- Deaths with an unknown cause should always be reported as an SAE. It should also be recorded in the CRF.
- A post-mortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results should be forwarded to the central trial office in Trondheim.

Deaths occurring after the protocol defined safety follow-up period after the administration of the last dose of study drug should be recorded in the CRF. If the death occurred as a result of an event that started after

the defined safety follow-up period and the event is considered to be due to a late onset toxicity to study drug, then it should also be reported as an SAE.

13.13 Reporting of serious adverse events and serious unexpected adverse reactions to the IRB and/or the Regulatory Authority

All SAEs must be reported, whether or not considered causally related to the investigational product. The Sponsor is responsible for informing the IRB and/or the Regulatory Authority of SAEs and SUSARs as per local requirements.

If any SAE occurs, investigators or other site personnel must inform appropriate Sponsor within one day i.e., immediately but no later than 24 hours of when he or she becomes aware of it.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform Sponsor representatives of any follow-up information on a previously reported SAE within one calendar day i.e., immediately but no later than 24 hours of when he or she becomes aware of it.

The reference document for definition of expectedness/listedness is the IB for durvalumab.

13.14 Reporting of serious adverse events to AstraZeneca

The central trial office in Trondheim is responsible for informing AstraZeneca (AZ) of SAEs. All SAEs have to be reported to AZ, whether or not considered causally related to durvalumab. SAEs related to durvalumab must be provided to AZ as individual case reports. SAEs unrelated to the durvalumab must be provided to AZ in quarterly reports.

At the end of the study a final summary listing of all SAEs notified to the regulatory authority and/or AZ during the study, must be provided to AZ to enable reconciliation of safety information held by AZ for durvalumab.

SAEs that do not require expedited reporting to the Regulatory Authority/IRB/IEC still need to be reported to AZ in quarterly reports.

Suspected Unexpected Serious Adverse Reactions (SUSARs) must be reported to AZ at the same time these events are notified to regulatory authorities.

13.14.1 Reporting of deaths to AstraZeneca

The central trial office will report all SAEs resulting in death or death of unknown cause to AstraZeneca via AEMailboxClinicalTrialTCS@astrazeneca.com within 7 calendar days of awareness or sooner when required (See Section 13.13).

13.15 Other events requiring reporting

13.15.1 Overdose

An overdose is defined as a patient receiving a dose of durvalumab in excess of that specified in the Investigator's Brochure, unless otherwise specified in this protocol.

Any overdose of a study patient with durvalumab, with or without associated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event to the sponsor. The sponsor must report these to AstraZeneca Patient Safety or designee using the designated Safety e-mailbox within 7 calendar days or sooner when required. If the overdose results in an AE, the AE must also be recorded as an AE. Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be recorded and reported as an SAE. There is currently no specific treatment in the event of an overdose of durvalumab. The investigator will use clinical judgment to treat any overdose.

13.15.2 Hepatic function abnormality

Hepatic function abnormality that fulfills the biochemical criteria of a potential Hy's Law case in a study patient, with or without associated clinical manifestations, is required to be reported as "hepatic function abnormal" within 24 hours of knowledge of the event to the sponsor. The Sponsor must report these

events to AstraZeneca Patient Safety using the designated Safety e-mailbox within 7 calendar days or sooner when required, unless a definitive underlying diagnosis for the abnormality (e.g., cholelithiasis or bile duct obstruction) that is unrelated to durvalumab has been confirmed. The criteria for a potential Hy's Law case is Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥3x Upper Limit of Normal (ULN) together with total bilirubin ≥2xULN at any timepoint during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

- If the definitive underlying diagnosis for the abnormality has been established and is unrelated to durvalumab, the decision to continue dosing of the study patient will be based on the clinical judgment of the investigator.
- If no definitive underlying diagnosis for the abnormality is established, dosing of the study patient must be interrupted immediately. Follow-up investigations and inquiries must be initiated by the investigational site without delay.

Each reported event of hepatic function abnormality will be followed by the investigator and evaluated by the sponsor and AstraZeneca.

13.15.3 Pregnancy

Maternal exposure

If a patient becomes pregnant during study participation, study treatment should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities or birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs during the study, the investigator or other site personnel should inform the sponsor within 1 day, i.e., immediately, but no later than 24 hours of when he or she becomes aware of it.

The sponsor will work with the Investigator to ensure that all relevant information is provided within 1 to 5 calendar days. Sponsor must report to AstraZeneca Patient Safety using the designated Safety e-mailbox within 7 calendar days or sooner when required, for pregnancies with SAEs and within 30 days for all other pregnancies. The same timelines apply when outcome information is available.

Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 180 days after the last dose of durvalumab + any drug combination therapy or 90 days after the last dose of durvalumab monotherapy, whichever is the longer time period.

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 180 days after the last dose of durvalumab + any drug combination therapy or 90 days after the last dose of durvalumab monotherapy, whichever is the longer time period should, if possible, be followed up and documented.

Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the investigator must obtain consent from the patient's partner. The local study team should adopt the generic ICF template in line with local procedures and submit it to the relevant IRB/REB/IEC prior to use.

13.16 Medication error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study drug that either causes harm to the patient or has the potential to cause harm to the patient.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or patient.

Medication error includes situations where an error

- Occurred
- Was identified and intercepted before the patient received the drug
- Did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error e.g. medication prepared incorrectly, even if it was not actually given to the patient
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated e.g. tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed e.g. kept in the fridge when it should be at room temperature
- Wrong patient received the medication
- Wrong drug administered to patient

Examples of events that do not require reporting as medication errors in clinical studies:

- Errors related to or resulting from IVRS/IWRS - including those that lead to one of the above listed events that would otherwise have been a medication error
- Patient accidentally missed drug dose(s) e.g. forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AZ product

Medication errors are not regarded as AEs, but AEs may occur as a consequence of the medication error. If a medication error occurs during the study, the Investigator or other site personnel must inform Sponsor within 1 day i.e., immediately but no later than 24 hours of when he or she becomes aware of it.
The Sponsor works with the Investigator to ensure that all relevant information is completed within 1 or 5 calendar days. The Sponsor must report to AstraZeneca Patient Safety using the designated Safety e-mailbox within 7 calendar days or sooner when required if there is an SAE associated with the medication error and within 30 days for all other medication errors.

14. Endpoints, statistical methods and sample size determination

14.1 Endpoints

Primary endpoint

- 1-year overall survival

Secondary endpoints

- 2-year, 3-year, 4-year and 5-year overall survival.
- Overall response rates
- Response rates in non-irradiated lesions
- Progression free survival
- Progression free survival in non-irradiated lesions
- Local control rates in the thorax
- Frequency and severity of adverse events
- Health-related quality of life

Exploratory endpoints

- Duration of severe adverse events
- Frequency and timing of brain metastases
- Assess cognitive function in the whole study cohort and compare cognitive function between patients who receive PCI and those who do not.
- Associations between outcomes of study treatment and biomarkers in tissue, blood and stool (e.g. ctDNA in blood, miRNA and gut microbiome).

14.2 Description of analysis sets

14.2.1 Safety analysis set

All patients who commence chemoimmunotherapy

14.2.2 Efficacy analysis set

The primary analyses will be performed on the intention to treat population, i.e. all eligible patients who are randomized. Secondarily, we will analyze patients who have received a minimum of three courses of chemoimmunotherapy (both arms) plus TRT (experimental arm) (per protocol population).

14.3 Methods of statistical analyses

14.3.1 Safety analyses

The frequency and severity of AEs will be compared between the treatment arms using the Pearson's Chi-square and Fisher's exact test as appropriate.

14.3.2 Efficacy analyses

For the primary endpoint, the Cox proportional hazards method will be used to compare survival between the treatment groups. Considering that median overall survival was 12-13 months in the two trials that established chemo-immunotherapy as treatment of ES SCLC, the study is designed to perform the primary survival analyses 14 months after last patient entry (to ensure that all survival data at 1 year are captured), which is a timepoint when we believe that the first signal of an effect of the experimental treatment can be seen. Additional survival analyses will be performed 2-, 3-, 4- and 5-year after last patient entry.

Median OS, PFS and time to progression in the brain will be estimated using the Kaplan-Meier method, and a Cox-model will be used for multivariable analyses adjusting for established prognostic factors in the target population (sex, PS, disease stage, presence of brain metastases and liver metastases) and age. Pearson's Chi-square test will be used to compare response rates (overall and in non-irradiated lesions), frequency of brain metastases, and location of metastases.

All HRQoL scores will be transformed to a scale of 0-100 according to the EORTC QLQ scoring manual. Mean scores will be compared at each assessment timepoint. A difference of 10 points is considered clinically relevant. Primary HRQoL-endpoints are dyspnea, global quality of life and physical function. All other HRQoL-scales will be included in complementary analyses.

14.3.3 Exploratory analyses

Cognitive function (MoCA-scores) will be compared using the Mann-Whitney test, and time until decline of MoCA-scores will be compared. Associations between biomarkers in tissue, blood and stool samples, and treatment outcomes, baseline characteristics, and survival will be investigated. A detailed project plan including biomarker and data analysis plan will be defined when sufficient biological material and clinical data to start the translational research have been collected.

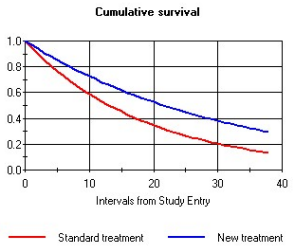
14.3.4 Interim analyses

The Safety and data monitoring committee will perform an interim analysis when 2/3 of the target number of patients (n≥85 in both arms) have completed a minimum of three chemotherapy courses (and TRT in the experimental arm). According to the O'Brien-Fleming approach, an alpha of 0.0054 will be allocated to the interim analyses. Consequently, enrolment will be stopped if the survival difference is statistically significant with a 2-sided p≤0.0054. If enrolment continues beyond the interim analysis, the significance level for the primary survival analysis is p≤0.0492.

14.4 Determination of sample size

The sample size calculation assumes an accrual period of 30 months and that the primary survival analysis is performed 14 months after last patient entry. Additional survival analyses will be performed 2, 3, 4 and 5 years after last patient entry. All patients will be followed for a maximum of 5 years when the final survival

analysis will be performed.



Furthermore, the calculation is based on a constant hazard ratio of 0.65, corresponding to median survival times of 13.10 months for the control group and 20.02 months for the experimental group, and 1-year survival rates of 53% in the control group and 66% in the experimental group. This effect was selected as an effect of clinical relevance and an effect of this magnitude might be anticipated if there is a synergistic effect of combining radiotherapy with durvalumab.

The criterion for significance (alpha) has been set at 5%. The test is 2-tailed, which means that an effect in either direction will be interpreted. For this study design, alpha and tails, the population effect size described above, and to have power of 80% to yield a statistically significant result, 128 patients are required in each treatment group.

Enrolment will continue until 128 or more patients in the control arm have completed minimum three chemo-immunotherapy courses, and minimum 128 patients in the experimental group have completed minimum three chemo-immunotherapy courses plus TRT of 30 Gy. We expect a loss to follow-up and inability to complete three courses (plus TRT in the experimental group) of maximum 15% and estimate that we need to enroll a total of 302 patients.

All eligible patients who are randomized will be included in the primary efficacy analyses (ITT-population). All patients who commence chemo-immunotherapy will be included in the toxicity analyses. In addition, we will perform analyses of the patients who complete minimum three chemo-immunotherapy courses (and TRT in the experimental arm) (per protocol population). The sample size calculation was performed using SPSS Sample Power v3.

15. Ethical and regulatory requirements

15.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH GCP, and applicable regulatory requirements Patient data protection.

15.2 Ethics and regulatory review

Approval from all relevant national and local regulatory authorities will be collected before enrolment starts.

15.3 Informed consent

Informed consent of each subject will be obtained through a written and verbal explanation process that addresses all elements required by ICH GCP. Sponsor will develop a core ICF for use by all investigators in the clinical study. The National Coordinating Investigator in each country will, based on this core ICF, be responsible for developing an ICF in all official languages in their country which complies with local and national laws and regulations.

The Principal Investigator(s) at each center will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study.
- Ensure each subject is notified that they are free to discontinue from the study at any time.
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided.
- Ensure each subject provides signed and dated ICF before conducting any procedure specifically for the study.
- Ensure the original, signed ICFs are stored in the Investigator's Site File.
- Ensure a copy of the signed ICF is given to the subject.

- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed due to study participation are described in the ICF.

15.4 Changes to the protocol and ICF

Study procedures will not be changed without the mutual agreement of the Principal Investigator and sponsor. Any changes will be documented in a study protocol amendment.

For a substantial change to the protocol, the sponsor will distribute amended versions of the protocol to all investigator(s). Before implementation, amended protocols, including revised ICD, must be approved by the relevant local and national regulatory authorities. Any non-substantial changes will be communicated to all relevant regulatory authorities.

15.5 Audits and inspections

Authorized representatives of a Competent Authority and IRB/REB/IEC may visit the centers to perform inspections, including source data verification. Likewise, the representatives from sponsor may visit the centers to perform an audit. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (ICH GCP), and any applicable regulatory requirements. The principal investigator at each study site will ensure that the inspectors and auditors will be provided with access to source data/documents.

16. Study management

16.1 Training of study site personnel

A site initiation visit will be performed at all sites before study start. Training will include walkthrough of the protocol, study procedures, CRF, study drug management, and reporting of AEs.
Furthermore, all personnel who will perform the MoCA test will need to complete the online training.
All study procedures will be described in a study procedure manual.

16.2 Monitoring of the study

16.2.1 Source data

The study will be monitored according to a separate monitoring plan.

16.3 Study timetable and end of study

We expect to enroll the first patient in Q1 2022, and to complete enrolment in Q2 2024. According to this schedule, the analyses for the primary endpoint will be performed in Q3 2025. All patients will be followed for a maximum of 5 years, and we expect to complete follow-up in Q2 2029.

17. Data management

The trial will be conducted in compliance with the protocol, ICH GCP and the applicable regulatory requirements. The staff at the central trial office at NTNU in Trondheim will oversee that data are collected and stored appropriately. The investigators must maintain adequate and accurate records to enable the study to be conducted according to protocol and fully documented, including but not limited to the protocol, protocol amendments, ICFs, and documentation of EC and governmental approval.

All patients will provide a written informed consent before any data are collected. The study personnel will enter data required by the protocol into the electronic, web-based Case report forms (WebCRF). Participants will be assigned a unique study ID at each site. All data recorded and transferred will be linked to this ID, no personal data will be stored in the CRF or transferred to the central trial office.

The web-based CRF has been developed in close collaboration between the Central Study Management, the protocol committee and the Unit for Applied Clinical Research, NTNU.

During study conduct, the data are stored on a secure server at the St. Olavs hospital with

restricted access. According to current regulations for clinical medical research, all data will be transferred to the Norwegian Centre for Research Data and stored for 15 years after study completion. All personally identifiable data will then be deleted.

The investigators are responsible for assuring that data entered in the CRF is complete, accurate, and that entry is performed in a timely manner, and no later than 2 weeks after each visit, procedure or AE. The CRF enables the central study management in Trondheim, in collaboration with monitors, to monitor data entry and send reminders if data are not entered within a reasonable timeframe.

The protocol specifies how SAEs, SUSARs and AESIs should be defined and reported. All SAE, SUSAR and AESI reports will immediately be reviewed by the medical personnel at the central trial office and complementary information will be requested when needed.

All sites will be monitored on a regular basis and minimum once per year during the study treatment period. The purpose is to verify that the patients' interests are secured, that the reported data are correct and complete, and that the trial is conducted in compliance with the trial protocol, general principles of Good Clinical Practice, and regulations by authorities. Any issues will be discussed with the site's Principal Investigator and the National Principal Investigator and may lead to closure of sites if not resolved.

18. List of references

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
2. Brustugun OT, Gronberg BH, Fjellbirkeland L, et al. Substantial nation-wide improvement in lung cancer relative survival in Norway from 2000 to 2016. Lung Cancer 2018;122:138-45.
3. Cancer Registry of Norway: Annual report of the National Lung Cancer Registry 2019.
4. Govindan R, Page N, Morgensztern D, et al. Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: analysis of the surveillance, epidemiologic, and end results database. J Clin Oncol 2006;24:4539-44.
5. Murray N, Turrisi AT, 3rd. A review of first-line treatment for small-cell lung cancer. J Thorac Oncol 2006;1:270-8.
6. Strand TE, Rostad H, Moller B, Norstein J. Survival after resection for primary lung cancer: a population based study of 3211 resected patients. Thorax 2006;61:710-5.
7. Resio BJ, Hoag J, Chiu A, et al. Prophylactic cranial irradiation is associated with improved survival following resection for limited stage small cell lung cancer. Journal of thoracic disease 2019;11:811-8.
8. Combs SE, Hancock JG, Boffa DJ, Decker RH, Detterbeck FC, Kim AW. Bolstering the case for lobectomy in stages I, II, and IIIA small-cell lung cancer using the National Cancer Data Base. J Thorac Oncol 2015;10:316-23.
9. Fruh M, De Ruysscher D, Popat S, et al. Small-cell lung cancer (SCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013;24 Suppl 6:vi99-105.
10. Noda K, Nishiwaki Y, Kawahara M, et al. Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. N Engl J Med 2002;346:85-91.
11. Schmittel A.H. SM, von Weikersthal F., Gauler T., Hortig P., Fischer J.R., Link H., Binder D., Eberhardt W., Keilholz U. Irinotecan plus carboplatin versus etoposide plus carboplatin in extensive disease small cell lung cancer: Results of the German randomized phase III trial. J Clin Oncol 27:15s, 2009 (suppl; abstr 8029).
12. Hanna N, Bunn PA, Jr., Langer C, et al. Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer. J Clin Oncol 2006;24:2038-43.
13. Lara PN, Jr., Natale R, Crowley J, et al. Phase III trial of irinotecan/cisplatin compared with etoposide/cisplatin in extensive-stage small-cell lung cancer: clinical and pharmacogenomic results from SWOG S0124. J Clin Oncol 2009;27:2530-5.
14. Xu F, Ren X, Chen Y, et al. Irinotecan-platinum combination therapy for previously untreated extensive-stage small cell lung cancer patients: a meta-analysis. BMC Cancer 2018;18:808.

15. Pignon JP, Arriagada R, Ihde DC, et al. A meta-analysis of thoracic radiotherapy for small-cell lung cancer. N Engl J Med 1992;327:1618-24.
16. Auperin A, Arriagada R, Pignon JP, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. N Engl J Med 1999;341:476-84.
17. Slotman B, Faivre-Finn C, Kramer G, et al. Prophylactic cranial irradiation in extensive small-cell lung cancer. N Engl J Med 2007;357:664-72.
18. Takahashi T, Yamanaka T, Seto T, et al. Prophylactic cranial irradiation versus observation in patients with extensive-disease small-cell lung cancer: a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 2017;18:663-71.
19. Gronberg BH, Halvorsen TO, Flotten O, et al. Randomized phase II trial comparing twice daily hyperfractionated with once daily hypofractionated thoracic radiotherapy in limited disease small cell lung cancer. Acta Oncol 2016;55:591-7.
20. Faivre-Finn C, Snee M, Ashcroft L, et al. Concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT): an open-label, phase 3, randomised, superiority trial. Lancet Oncol 2017;18:1116-25.
21. Howlader N, Forjaz G, Mooradian MJ, et al. The Effect of Advances in Lung-Cancer Treatment on Population Mortality. N Engl J Med 2020;383:640-9.
22. Dunn GP, Old LJ, Schreiber RD. The three Es of cancer immunoediting. Annu Rev Immunol 2004;22:329-60.
23. Keir ME, Butte MJ, Freeman GJ, Sharpe AH. PD-1 and its ligands in tolerance and immunity. Annu Rev Immunol 2008;26:677-704.
24. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med 2015;373:123-35.
25. Gandhi L, Garassino MC. Pembrolizumab plus Chemotherapy in Lung Cancer. N Engl J Med 2018;379:e18.
26. Reck M, Brahmer JR. Pembrolizumab in Non-Small-Cell Lung Cancer. N Engl J Med 2017;376:997.
27. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. N Engl J Med 2017;377:1919-29.
28. Ott PA, Elez E, Hiret S, et al. Pembrolizumab in Patients With Extensive-Stage Small-Cell Lung Cancer: Results From the Phase Ib KEYNOTE-028 Study. J Clin Oncol 2017:Jco2017725069.
29. Antonia SJ, J.A. Lopez-Martin, et al., Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. Lancet Oncol, 2016. 17(7): p. 883-895.
30. Goldman J, A. D, Antonia S, et al. Safety and antitumor activity of durvalumab monotherapy in patients with pretreated extensive disease small-cell lung cancer (ED-SCLC). J Clin Oncol 2018;36.
31. Cho DC, Mahipal A, Dowlati A, Chow WA. Safety and clinical activity of durvalumab in combination with tremelimumab in extensive disease small-cell lung cancer (ED-SCLC). J Clin Oncol 2018;36.
32. Bondarenko I, Juan-Vidal O, Pajkos G. Preliminary efficacy of durvalumab plus tremelimumab in platinumrefractory/resistant ED-SCLC from arm A of the phase II BALTICstudy. Ann Oncol 2018;29.
33. Pujol JL, Greillier L, Audigier-Valette C, et al. A Randomized Non-Comparative Phase II Study of Anti-Programmed Cell Death-Ligand 1 Atezolizumab or Chemotherapy as Second-Line Therapy in Patients With Small Cell Lung Cancer: Results From the IFCT-1603 Trial. J Thorac Oncol 2019;14:903-13.
34. Owonikoko TK, Kim HR, Govindan R. Nivolumab (nivo) plus ipilimumab (ipi), nivo, or placebo (pbo) as maintenance therapy in patients (pts) with extensive disease small cell lung cancer (ED-SCLC) after first-line (1L) platinum-based chemotherapy (chemo): Results from the double-blind, randomized phase III CheckMate 451 study. Ann Oncol 2019;30.
35. Horn L, Reck M, Gettinger SN, et al. CheckMate 331: An open-label, randomized phase III trial of nivolumab versus chemotherapy in patients (pts) with relapsed small cell lung cancer (SCLC) after first-line platinum-based chemotherapy (PT-DC). Journal of Clinical Oncology 2016;34:TPS8578-TPS.
36. Horn L, Mansfield AS, Szczesna A, et al. First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. N Engl J Med 2018;379:2220-9.

37. Goldman JW, Dvorkin M, Chen Y, et al. Durvalumab, with or without tremelimumab, plus platinum-etoposide versus platinum-etoposide alone in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): updated results from a randomised, controlled, open-label, phase 3 trial. Lancet Oncol 2020.
38. Rudin CM, Awad MM, Navarro A, et al. Pembrolizumab or Placebo Plus Etoposide and Platinum as First-Line Therapy for Extensive-Stage Small-Cell Lung Cancer: Randomized, Double-Blind, Phase III KEYNOTE-604 Study. J Clin Oncol 2020;38:2369-79.
39. Iams WT, Shiuan E, Meador CB, et al. Improved Prognosis and Increased Tumor-Infiltrating Lymphocytes in Patients Who Have SCLC With Neurologic Paraneoplastic Syndromes. J Thorac Oncol 2019;14:1970-81.
40. Dalmau J, Geis C, Graus F. Autoantibodies to Synaptic Receptors and Neuronal Cell Surface Proteins in Autoimmune Diseases of the Central Nervous System. Physiol Rev 2017;97:839-87.
41. Titulaer MJ, Klooster R, Potman M, et al. SOX antibodies in small-cell lung cancer and Lambert-Eaton myasthenic syndrome: frequency and relation with survival. J Clin Oncol 2009;27:4260-7.
42. Hoftberger R, van Sonderen A, Leypoldt F, et al. Encephalitis and AMPA receptor antibodies: Novel findings in a case series of 22 patients. Neurology 2015;84:2403-12.
43. Maddison P, Gozzard P, Grainge MJ, Lang B. Long-term survival in paraneoplastic Lambert-Eaton myasthenic syndrome. Neurology 2017;88:1334-9.
44. Vural B, Chen LC, Saip P, et al. Frequency of SOX Group B (SOX1, 2, 3) and ZIC2 antibodies in Turkish patients with small cell lung carcinoma and their correlation with clinical parameters. Cancer 2005;103:2575-83.
45. Wirtz PW, Lang B, Graus F, et al. P/Q-type calcium channel antibodies, Lambert-Eaton myasthenic syndrome and survival in small cell lung cancer. J Neuroimmunol 2005;164:161-5.
46. van Coevorden-Hameete MH, van Beuningen SFB, Perrenoud M, et al. Antibodies to TRIM46 are associated with paraneoplastic neurological syndromes. Ann Clin Transl Neurol 2017;4:680-6.
47. van Coevorden-Hameete MH, de Bruijn M, de Graaff E, et al. The expanded clinical spectrum of anti-GABABR encephalitis and added value of KCTD16 autoantibodies. Brain 2019;142:1631-43.
48. Slotman BJ, van Tinteren H, Praag JO, et al. Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial. Lancet 2015;385:36-42.
49. Liu Y, Dong Y, Kong L, Shi F, Zhu H, Yu J. Abscopal effect of radiotherapy combined with immune checkpoint inhibitors. J Hematol Oncol 2018;11:104.
50. Weichselbaum RR, Liang H, Deng L, Fu YX. Radiotherapy and immunotherapy: a beneficial liaison? Nature reviews Clinical oncology 2017;14:365-79.
51. Formenti SC, Demaria S. Combining radiotherapy and cancer immunotherapy: a paradigm shift. J Natl Cancer Inst 2013;105:256-65.
52. Dovedi SJ, Adlard AL, Lipowska-Bhalla G, et al. Acquired resistance to fractionated radiotherapy can be overcome by concurrent PD-L1 blockade. Cancer Res 2014;74:5458-68.
53. Sharabi AB, Lim M, DeWeese TL, Drake CG. Radiation and checkpoint blockade immunotherapy: radiosensitisation and potential mechanisms of synergy. Lancet Oncol 2015;16:e498-509.
54. Hendriks LEL, Menis J, De Ruysscher DKM, Reck M. Combination of Immunotherapy and Radiotherapy-The Next Magic Step in the Management of Lung Cancer? J Thorac Oncol 2020;15:166-9.
55. Welsh JW, Heymach JV, Chen D, et al. Phase I Trial of Pembrolizumab and Radiation Therapy after Induction Chemotherapy for Extensive-Stage Small Cell Lung Cancer. J Thorac Oncol 2020;15:266-73.
56. Lin SH, Lin Y, Yao L, et al. Phase II Trial of Concurrent Atezolizumab With Chemoradiation for Unresectable NSCLC. J Thorac Oncol 2020;15:248-57.
57. McBride S, Sherman E, Tsai CJ, et al. Randomized Phase II Trial of Nivolumab With Stereotactic Body Radiotherapy Versus Nivolumab Alone in Metastatic Head and Neck Squamous Cell Carcinoma. J Clin Oncol 2020:JCO2000290.
58. Mok T RM, Horn L, et al. IMpower133: Primary efficacy and safety + CNS-related adverse events in a phase I/III study of first-line (1L) atezolizumab + carboplatin + etoposide in extensive-stage SCLC (ES-SCLC). Annals of Oncology 29:LBA1, 2018.
59. Halvorsen TO, Herje M, Levin N, et al. Tumour size reduction after the first chemotherapy-course and outcomes of chemoradiotherapy in limited disease small-cell lung cancer. Lung Cancer 2016;102:9-14.

60. Levy A, Massard C, Soria JC, Deutsch E. Concurrent irradiation with the anti-programmed cell death ligand-1 immune checkpoint blocker durvalumab: Single centre subset analysis from a phase 1/2 trial. Eur J Cancer 2016;68:156-62.
61. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365-76.
62. Bergman B, Aaronson NK, Ahmedzai S, Kaasa S, Sullivan M. The EORTC QLQ-LC13: a modular supplement to the EORTC Core Quality of Life Questionnaire (QLQ-C30) for use in lung cancer clinical trials. EORTC Study Group on Quality of Life. Eur J Cancer 1994;30A:635-42.
63. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005;53:695-9.
64. Rudin CM, Poirier JT, Byers LA, et al. Molecular subtypes of small cell lung cancer: a synthesis of human and mouse model data. Nat Rev Cancer 2019;19:289-97.
65. Gay CM, Stewart CA, Park EM, et al. Patterns of transcription factor programs and immune pathway activation define four major subtypes of SCLC with distinct therapeutic vulnerabilities. Cancer Cell 2021.
66. Tlemsani C, Takahashi N, Pongor L, et al. Whole-exome sequencing reveals germline-mutated small cell lung cancer subtype with favorable response to DNA repair-targeted therapies. Sci Transl Med 2021;13.
67. Goldberg SB, Narayan A, Kole AJ, et al. Early Assessment of Lung Cancer Immunotherapy Response via Circulating Tumor DNA. Clin Cancer Res 2018;24:1872-80.
68. Yanaihara N, Caplen N, Bowman E, et al. Unique microRNA molecular profiles in lung cancer diagnosis and prognosis. Cancer Cell 2006;9:189-98.
69. Pierrard J, Seront E. Impact of the gut microbiome on immune checkpoint inhibitor efficacy-a systematic review. Curr Oncol 2019;26:395-403.
70. Routy B, Le Chatelier E, Derosa L, et al. Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. Science (New York, NY) 2018;359:91-7.