Multimodality Treatment in Stage III Non-small Cell Lung Cancer (NSCLC)

NCT-Nummer:
NCT04245514

Studienbeginn:
Juli 2020

Letztes Update:
19.08.2020

Wirkstoff:
Durvalumab
Indikation (Clinical Trials):
Lung Neoplasms, Carcinoma, Non-Small-Cell Lung

Geschlecht:
Alle

Altersgruppe:
Erwachsene (18+)

Phase:
Phase 2

Sponsor:
Swiss Group for Clinical Cancer Research

Collaborator:
-

Studien-Informationen

Detailed Description:

In resectable locally advanced lung cancer there is an urgent need for more efficacious therapy, since most of the patients will eventually have a relapse and will die of the disease. Distant metastases are the main site of recurrence. Therefore, the most promising treatment strategy is to better eliminate micrometastases present at the time of diagnosis through improved systemic treatment. In this regard, the SAKK 16/14 trial is investigating the efficacy of the anti-PD-L1 inhibitor durvalumab before and after surgery added to standard neoadjuvant chemotherapy with cisplatin/docetaxel. It has just completed accrual as of Q1 2019.

The primary aim of the SAKK 16/18 trial is to evaluate the efficacy and safety of adding immune-modulatory radiotherapy to the SAKK 16/14 treatment regimen by combining it with neoadjuvant immunotherapy. Due to the lack of evidence for an optimal immune-modulatory radiotherapy regimen we test 3 different radiotherapy regimens to investigate differences in efficacy and tolerability as key exploratory endpoint.

Neoadjuvant therapy is the optimal setting to test the combination of immune-modulatory radiotherapy and immune checkpoint inhibitor therapy. Resection of the primary tumor and mediastinal lymph nodes will allow to investigate pathological responses and nodal downstaging at an early time point. Furthermore, this setting allows for extensive translational research evaluating cellular and molecular mechanisms of anti-tumor immune response.

SAKK 16/18 is a prospective, multicenter, phase II trial with 3 radiotherapy cohorts.

The treatment consists of

- Neoadjuvant chemotherapy with cisplatin and docetaxel: 3 cycles of 21 days

- Neoadjuvant immunotherapy with durvalumab: 1 cycle

- Neoadjuvant immune-modulatory radiotherapy

- Concurrent with neoadjuvant immunotherapy

- Random assignment to one of the following fractionation regimens:

- 20x2 Gy (weekdaily, 4 weeks)

- 5x5 Gy (weekdaily, 1 week)

- 3x8 Gy (on alternate days, 1 week)

- Surgery

o Between 4 and 6 weeks after the application of durvalumab (independent of the radiotherapy regimen)

- If indicated: Postoperative radiotherapy (should start between 3 to 6 weeks after surgery)

- Adjuvant immunotherapy with durvalumab: 13 cycles of 28 days

Ein-/Ausschlusskriterien

Inclusion Criteria:

- Written informed consent according to ICH-GCP regulations before registration and prior to any trial specific procedures.

- Histologically (cytology is accepted if histology is not possible) confirmed NSCLC (adeno-,

squamous-, large cell carcinoma, or NSCLC not otherwise specified (NOS)) irrespective of genomic aberrations or PD-L1 expression status.

- Tumor stage T1-4>7 N2 M0 (i.e. T1-3 N2 or T4 N2 but T4 only allowed if due to size > 7cm, not allowed if due to invasion or nodule in different ipsilateral lobe), according to the TNM classification, 8th edition, December 2016 (see Appendix 2). Mediastinal lymph node staging has to follow the process chart.

- Tumor is considered resectable based on a multidisciplinary tumor board decision made before neoadjuvant treatment. Resectable is when a complete resection can be achieved according to Rami-Porta

- Patients with a prior malignancy (except NSCLC) and treated with curative intention are eligible if all treatment of that malignancy was completed at least 2 years before registration and the patient has no evidence of disease at registration. Less than 2 years is acceptable for malignancies with low risk of recurrence and/or no late recurrence, after consultation with CI.

- Measurable disease per RECIST v1.1 criteria by PET/CT with contrast enhanced CT-scan.

- Tumor tissue is available for the mandatory translational research (formalin-fixed; preferably histology, cytology allowed if histology is not possible)

- Age 18-75 years at time of registration

- WHO performance status 0-1

- Adequate bone marrow function: absolute neutrophil count ≥ 1.5 x 109/L, platelet count ≥ 100 x 109/L, hemoglobin ≥ 90 g/L (transfusion allowed)

- Adequate hepatic function: total bilirubin ≤ 1.5 x ULN (except for patients with Gilbert's disease ≤ 3.0 x ULN), AST and ALT ≤ 1.5 x ULN, AP ≤ 2.5 x ULN.

- Adequate renal function: calculated creatinine clearance ≥ 60 mL/min, according to the formula of Cockcroft-Gault

- Appropriate lung function based on the ESTS guidelines:

- For pneumonectomy: FEV1 and DLCO ≥80%. If one of both <80%, an exercise test peak VO2 >75% or 20ml/kg/min is needed

- For resection less than pneumonectomy (resection up to the calculated extent): exercise test peak VO2 ≥35% or ≥10ml/kg/min, with predicted postoperative FEV1 and DLCO ≥ 30%.

- Adequate cardiac function according to investigator's decision based on evaluation of risk according to NYHA classification

- Women of childbearing potential must use highly effective contraception, are not pregnant or lactating and agree not to become pregnant during trial treatment and until 90 days after the last dose of investigational drug. A negative pregnancy test performed within 7 days before registration is required for all women of childbearing potential.

- Men agree not to donate sperm or to father a child during trial treatment and until 90 days after the last dose of investigational drug.

Exclusion criteria:

- Presence of any distant metastasis or N3 disease. Brain metastases have to be excluded by CT or MRI.

- Sulcus superior tumors (Pancoast tumors) or T4 for any other reason than size >7cm.

- Any previous treatment for NSCLC

- Any previous treatment with immune checkpoint inhibitors, including durvalumab

- Previous radiotherapy to the chest (with the exception of tangential breast irradiation with minimal dose to lung and mediastinum, and superficial orthovoltage or electron irradiation of localized skin lesions)

- Concomitant or recent (within 30 days of registration) treatment with any other experimental drug and/or enrollment in another clinical trial.

- Concomitant use of other anti-cancer drugs or radiotherapy.

- Severe or uncontrolled cardiovascular disease (congestive heart failure NYHA III or IV) unstable angina pectoris, history of myocardial infarction within the last three months, serious arrhythmias requiring medication (with exception of atrial fibrillation or paroxysmal supraventricular tachycardia), uncontrolled hypertension.

- Preexisting peripheral neuropathy (> Grade 1)

- Body weight less than 30 kg

- Known history of human immunodeficiency virus (HIV) or active chronic Hepatitis C or Hepatitis B virus infection or any uncontrolled active systemic infection requiring intravenous (iv) antimicrobial treatment.

- Known history of allogeneic organ transplant

- Active autoimmune disease or a syndrome requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease. Exceptions: vitiligo, resolved childhood asthma/atopy, hypothyroidism stable on hormone replacement, Sjögren's syndrome

- Active or prior documented inflammatory bowel disease (e.g. Crohn's disease, ulcerative colitis)

- Concomitant or prior use of immunosuppressive medication within 28 days before registration, with the exceptions of intranasal and inhaled corticosteroids, or systemic corticosteroids which must not exceed 10 mg/day of prednisone or a dose equivalent corticosteroid, and the premedication for chemotherapy

- Any concomitant drugs contraindicated for use with the trial drugs according to the approved

product information.

- Known hypersensitivity to trial drugs (cisplatin and docetaxel, durvalumab) or to any excipient

- Any other serious underlying medical, psychiatric, psychological, familial or geographical condition, which in the judgment of the investigator may interfere with the planned staging, treatment and follow-up, affect patient compliance or place the patient at high risk from treatment-related complications.

Studien-Rationale

Primary outcome:

1. Event-free survival (EFS) at 12 months (Time Frame - at 12 months):
EFS is defined as time from registration to one of the following events, whichever occurs first: Relapse or progression according to RECIST 1.1 criteria. Second tumor Death due to any cause Patients not experiencing an event will be censored at the date of last tumor assessment before starting a subsequent treatment, if any. As a sensitivity analysis, the primary endpoint will also be calculated according to the following definition of an event: Progression during neoadjuvant treatment leading to inoperability Recurrence of loco-regional disease after surgery Appearance of metastases at any localization Second tumor Death due to any cause

Secondary outcome:

1. Event-free survival (EFS) (Time Frame - From the date of registration until the date of progressive disease, relapse, second tumor or death, whichever occurs first, assessed up to 20 years after registration):
EFS is defined as time from registration to one of the following events, whichever occurs first: Relapse or progression according to RECIST 1.1 criteria Second tumor Death due to any cause Patients not experiencing an event will be censored at the date of last tumor assessment before starting a subsequent treatment, if any. As a sensitivity analysis, the primary endpoint will also be calculated according to the following definition of an event: Progression during neoadjuvant treatment leading to inoperability Recurrence of loco-regional disease after surgery Appearance of metastases at any localization Second tumor Death due to any cause

2. Recurrence-free survival (RFS) after R0 resection (Time Frame - From the date of surgery until the date of recurrence of loco-regional disease, appearance of metastases, or death, whichever occurs first, assessed up to 20 years after registration):
RFS after R0 resection is defined as the time from surgery until one of the following events, whichever comes first: Recurrence of loco-regional disease Appearance of metastases at any localization Death Patients not experiencing an event will be censored at the date of the last available assessment before initiation of a subsequent treatment, if any. This endpoint will only be calculated for patients with R0 resection.

3. Overall survival (OS) (Time Frame - From the date of registration until the date of death from any cause, assessed up to 20 years after registration):
OS is defined as time from registration until death due to any cause. Patients not experiencing an

event will be censored at the last date they were known to be alive.

4. Objective response (OR) after neoadjuvant chemotherapy (Time Frame - At the date of tumor assessment after neoadjuvant chemotherapy, estimated at approximately 9 weeks post-baseline):
OR after neoadjuvant chemotherapy is defined as complete response (CR) or partial response (PR) after the end of neoadjuvant chemotherapy. Response will be evaluated according to RECIST 1.1 criteria. Patients without response assessment after the end of neoadjuvant chemotherapy will be regarded as having a non-evaluable response (NE) and shall be considered as failures for this endpoint.

5. OR after neoadjuvant immuno-radiotherapy (Time Frame - At the date of tumor assessment after neoadjuvant immune-radiotherapy, estimated at approximately 13 weeks post-baseline):
OR after neoadjuvant immuno-radiotherapy is defined as complete response (CR) or partial response (PR) after the end of neoadjuvant immuno-radiotherapy. Response will be evaluated according to RECIST 1.1 criteria. Patients without response assessment after the end of neoadjuvant immuno-radiotherapy will be regarded as having a non-evaluable response (NE) and shall be considered as failures for this endpoint.

6. Pathological Complete Response (pCR) (Time Frame - At the date of tumor assessment after surgery, estimated at approximately 15 weeks post-baseline):
pCR is defined as complete tumor regression with no evidence of vital tumor cells in the sections of the primary lesion and mediastinal lymph nodes after surgery [69]. Patients who were not operated will not be taken into consideration for this endpoint. Results from Central Pathology will be used.

7. Major pathological response (MPR) (Time Frame - At the date of tumor assessment after surgery, estimated at approximately 15 weeks post-baseline):
Major pathologic response is defined as the presence of 10% or less of vital tumor cells in the sections of the primary lesion and/or mediastinal lymph nodes presenting focal microscopic disease after surgery [66]. Patients who were not operated will not be taken into consideration for this endpoint. Results from Central Pathology will be used.

8. Nodal down-staging to < ypN2 (Time Frame - At the date of tumor assessment after surgery, estimated at approximately 15 weeks post-baseline):
Nodal down-staging to < ypN2 is defined as the case where after the surgery the remaining node status of the patients according to the TNM cancer staging system is less than N2 (N0/1). Patients who were not operated will not be taken into consideration for this endpoint.

9. Complete resection (Time Frame - At the date of tumor assessment after surgery, estimated at approximately 15 weeks post-baseline):
Complete resection is defined as fulfillment of all the following criteria, according to [70]: free resection margins proved microscopically (R0 resection) systematic nodal dissection or lobe-specific systematic nodal dissection no extracapsular nodal extension of the tumor the highest mediastinal node removed must be negative Patients who were not operated will not be taken into consideration for this endpoint.

Geprüfte Regime

- Durvalumab:
  Immunotherapy
- Radiotherapy:
  Immune-modulatory radiotherapy to the primary tumor, with either Cohort A: 20 x 2 Gy weekdaily Cohort B: 5 x 5 Gy weekdaily Cohort C: 3 x 8 Gy q2d

Studienleiter

Sacha Rothschild, MD
Study Chair
Universitätsspital Basel

Kontakt

Catherine Berset, PhD
Kontakt:
Phone: +41 31 389 91 91
E-Mail: trials@sakk.ch

Studienlocations (3 von 13)

Kantonsspital Aarau
CH-5001 Aarau
Switzerland

Status: Rekrutierend

Kantonsspital Baden
5404 Baden
Switzerland

Status: Rekrutierend

St. Claraspital Basel
4016 Basel
Switzerland

Status: Rekrutierend

Universitaetsspital Basel

4031 Basel
Switzerland

Status: Rekrutierend

IOSI Ospedale Regionale di Bellinzona e Valli
6500 Bellinzona
Switzerland

Status: Rekrutierend

Inselspital
3010 Bern
Switzerland

Status: Rekrutierend

Kantonsspital Graubuenden
CH-7000 Chur
Switzerland

Status: Rekrutierend

Hôpitaux Universitaires de Genève
1211 Genève
Switzerland

Status: Rekrutierend

Kantonsspital - St. Gallen
CH-9007 St. Gallen
Switzerland

Status: Rekrutierend

Regionalspital Thun
3600 Thun
Switzerland

Status: Rekrutierend

Universitätsspital Zuerich
8091 Zurich

Switzerland

Status: Rekrutierend

Hirslanden Onkozentrum Zürich
8032 Zürich
Switzerland

Status: Rekrutierend

Stadtspital Triemli
8063 Zürich
Switzerland

Status: Rekrutierend

Quelle: ClinicalTrials.gov