SAKK 16/14 – Anti-PD-L1 antibody durvalumab (MEDI4736) in addition to neoadjuvant chemotherapy in patients with stage IIIA(N2) non-small cell lung cancer (NSCLC). A multicenter single-arm phase II trial.

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Background

- Approximately 15-20% of non-small cell lung cancer (NSCLC) patients initially present with locally advanced stage IIIA(N2) disease.
- Platinum-based chemotherapy in addition to surgery (neoadjuvant or adjuvant) improves survival by about 4% in stage IB-III NSCLC.[1]
- Preoperative chemotherapy appears to be better tolerated than adjuvant chemotherapy, with a high compliance of 90-95%.[2]
- Surgery after neoadjuvant therapy is feasible in selected patients with N2 disease at experienced centers with recorded low perioperative mortality.[3-5]
- Previous SAKK trials established a standard of care for stage IIIA(N2):
  - 3 cycles of neoadjuvant chemotherapy with cisplatin and docetaxel followed by surgery (SAKK 16/96 and SAKK 16/00).[4,5]
  - Addition of neoadjuvant radiotherapy does not improve outcome.[5]
- Immune checkpoint inhibitors showed promising results in palliative treatment of NSCLC and are an approved option for second-line therapy.[6-8]
- In the PACIFIC trial Durvalumab significantly improved progression-free survival as consolidation therapy after definitive chemoradiotherapy in unresectable stage III NSCLC.[9]

Objective

The objective of the trial is to demonstrate that the addition of perioperative immunotherapy with the anti-programmed cell death ligand 1 (PD-L1) antibody durvalumab (MEDI4736) to standard chemotherapy with cisplatin/docetaxel in primary resectable stage IIIA(N2) NSCLC is efficacious and feasible.

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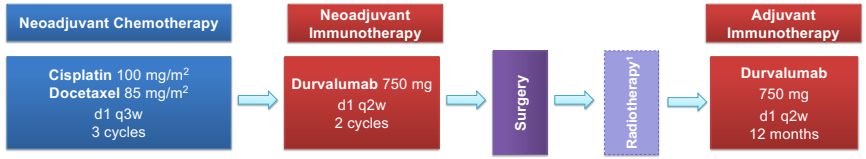
Trial Design

Multicenter, single-arm, phase II trial



[1]Postoperative Radiotherapy for patients with R1/R2 resection

Statistical Considerations

- A rate of EFS at 12 months after registration ≤ 48% (based on previous SAKK trials[4,5]) is considered uninteresting while a rate ≥ 65% is considered promising
- According to a single-stage phase II design based on survival rate at a specific time-point, 64 patients are needed to obtain a power of 80% with a significance level of 5%.
- Assuming a 5% rate of non-evaluable patients for the primary endpoint, the target sample size is increased to 68 patients.

Study Endpoints

- ***Primary endpoint***
  - Event-free survival (EFS) at 12 months
- ***Secondary endpoints***
  - EFS
  - Overall survival (OS)
  - Objective response (OR) after neoadjuvant chemotherapy
  - OR after neoadjuvant immunotherapy
  - Pathological complete response (pCR)
  - Major pathological response (10% or less residual viable tumor)
  - Rate of nodal down-staging to < ypN2
  - Complete resection
  - Pattern of recurrence (local, loco-regional, distant)
  - Adverse events (AEs)
  - Postoperative 30-day mortality
- ***Additional research questions***
  - Comparison of the tumor immunome at the time of diagnosis (treatment-naive) and at the time of tumor resection (after neoadjuvant chemo- and immunotherapy)
  - Investigation of efficacy outcome parameters (EFS, OR, OS) in relation to tissue expression of PD-L1 (tumor and immune cells)
  - Investigation of biomarkers for anti-PD-L1 treatment and their relation to efficacy outcome parameters of interest (EFS, OS and OR after neoadjuvant immunotherapy)

Eligibility Criteria

- ***Major inclusion criteria***
  - Pathologically proven NSCLC irrespective of genomic aberrations or PD-L1 expression status
  - Tumor tissue available for the mandatory translational research
  - Tumor stage T1-3N2M0 (stage IIIA(N2)) according to TNM 7th edition
  - Tumor is considered resectable based on a multidisciplinary tumor board decision
  - Age 18-75 years
  - WHO performance status 0-1
  - Appropriate lung function based on the ESTS guidelines
- ***Major exclusion criteria***
  - Previous or concomitant malignancy within 5 years prior registration
  - Previous therapy for NSCLC
  - Previous treatment with a PD-1 or PD-L1 inhibitor
  - Previous radiotherapy to the chest
  - Preexisting peripheral neuropathy
  - Active autoimmune disease requiring systemic treatment within the past 3 months
  - Documented history of clinically severe autoimmune disease
  - History of primary immunodeficiency, allogeneic organ transplant or previous clinical diagnosis of tuberculosis; known evidence of acute or chronic hepatitis B, hepatitis C or HIV infection

Oversight of Study

- Accrual / Duration
  - March 2016 initiation of first site.
  - 68 patients, originally expected within 3 years.
  - Current accrual (April 5, 2018): 47 patients.
  - Last patient last treatment expected in Q2/3 2020.
- Interim safety analysis
  - First 25 operated patients.
  - 30-day post-operative mortality < 10%,
  - 1 patient died due to bleeding complication,
  - Decision was to continue the trial as per protocol.

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