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-II 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 III(N2): • 3 cycles of neoadjuvant chemotherapy with cisplatin and docetaxel followed by surgery (SAKK 16/06 and SAKK 16/00).1,4-5 • 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.3

Objective

The objective of the trial is to demonstrate that the addition of perioperative chemotherapy 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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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 chemoradiotherapy) • 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)

Trial Design

Neoadjuvant Chemotherapy

Cisplatin 100 mg/m²
d1 q2w
3 cycles

Docetaxel 65 mg/m²
d1 q2w
3 cycles

Neoadjuvant Immunotherapy

Durvalumab 750 mg
d1 q2w
2 cycles

Surgery

Radiation

Adjuvant Immunotherapy

Durvalumab 750 mg
d1 q2w
12 months

*Postoperative Radiotherapy for patients with R1/R2 resection

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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 concurrent 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

Statistical Considerations

• A rate of EFS at 12 months after registration ≤ 48% (based on previous SAKK trials4-5) 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.

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.

References


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