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SAKK - SWISS GROUP FOR CLINICAL CANCER RESEARCH

Protocol SAKK 16/14

Anti-PD-L1 antibody 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.

Protocol version:	Version 3.0, including amendments 1 and 2, 04.08.2017
SNCTP No.:	SNCTP000001480
Study type:	Clinical trial with Investigational Medicinal Product (IMP)
Categorization:	Risk category C according to the Human Research Act (HRA) and its ordinance KlinV/Oclin

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Sponsor:	Swiss Group for Clinical Cancer Research Bern, Switzerland

PROTOCOL SIGN-OFF PAGE

SAKK 16/14. Anti-PD-L1 antibody 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.

The protocol SAKK 16/14 was accepted by the SAKK Board on 27.01.2015 and has passed the recommended review process for SAKK trials.

The final protocol is dated 13.10.2015. Protocol version 2.0 including amendment 1 is dated 13.12.2016. Protocol version 3.0, including amendments 1 and 2, is dated 04.08.2017.

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PROTOCOL SIGN-OFF PAGE PROTOCOL VERSION 3.0 FOR THE PRINCIPAL INVESTIGATOR

SAKK 16/14. Anti-PD-L1 antibody 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.

Principal Investigator in: _____

Having read and understood protocol VERSION 3.0 including amendments 1 and 2, I agree to conduct the trial as specified in the protocol.

Name: _____ Title: _____

Date: _____ Signature: _____

ABBREVIATIONS

ADA	Antidrug antibodies
AE	Adverse event
AESI	AE of special interest
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
AUC	Area under the curve
CD	Cluster of differentiation
CI	Confidence interval
CR	Complete response
CrCl	Creatine clearance
CRF	Case report form
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
DLCO	Diffusing capacity of the lung for carbone monoxide
DSUR	Development Safety Update report
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic CRF
EDC	Electronic data capture
EFS	Event-free survival
FAS	Full analysis set
FDG	Fludeoxyglucose (^{18}F)
FEV1	Force expiratory volume in 1 s
FFPE	Formalin-fixed paraffin-embedded
GCP	Good Clinical Practice
G-CSF	Granulocyte-colony stimulating factor
GGT	Gamma-glutamyltransferase
HE	Hematoxylin and eosin
HFV	Humanforschungsverordnung
HR	Hazard ratio
HRA	Human research act
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IDMC	Independent data monitoring committee
Ig	Immunoglobulin
IHC	Immunohistochemistry
ILD	Interstitial lung disease
IMP	Investigational medicinal product
INR	International normalized ratio
irAE	Immune-related AE
i.v.	Intravenous
KlinV	Verordnung über klinische Versuche in der Humanforschung
KOFAM	Koordinationsstelle Forschung am Menschen
mAb	Monoclonal antibody
MRI	Magnetic resonance imaging
LLN	Lower limit of normal

NCI	National Cancer Institute
NE	Non-evaluable
NGS	Next-generation sequencing
NSCLC	Non-small cell lung cancer
NTL	Non-target lesions
OClin	Ordonnance sur les essais cliniques dans le cadre de la recherche sur l'être humain
OR	Objective response
ORH	Ordonnance relative à la recherche sur l'être humain
ORR	Objective response rate
OS	Overall survival
OV-HFG	Organisationsverordnung zum Humanforschungsgesetz
pCR	Pathological complete response
PD	Progressive disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death ligand 1
PET	Positron emission tomography
PIS/IC	Patient information sheet and informed consent form
PK	Pharmacokinetics
p.o.	Per os (orally)
PP	Per protocol
ppo	Predictive postoperative
PQC	Product quality complaint
PR	Partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAR	Serious adverse reaction
SAKK	Schweizerische Arbeitsgemeinschaft für Klinische Krebsforschung / Swiss Group for Clinical Cancer Research
SAKK CC	SAKK Coordinating Center
SAP	Statistical analysis Plan
SD	Stable Disease
SDV	Source data verification
SNCTP	Swiss National Clinical Trials Portal
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
SUVA	Schweizerische Unfallversicherungsanstalt
TB	Total bilirubin
TL	Target lesions
TNF-α	Tumor necrosis factor-α
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
UPN	Unique patient number
VO2	Oxygen consumption
WBC	White blood cells
WHO	World Health Organization

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1 TRIAL OVERVIEW SAKK 16/14

SAKK 16/14. Anti-PD-L1 antibody 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.

Sponsor: Swiss Group for Clinical Cancer Research (SAKK)

Trial registry No.: SNCTP No.: SNCTP000001480
Clinicaltrials.gov No.: NCT02572843

Coordinating investigator: Sacha Rothschild, MD PhD, University Hospital, Basel, Switzerland

TRIAL PHASE AND CATEGORY

This is a phase II clinical trial with IMP.

The IMP MEDI4736 (durvalumab) is an investigational product without marketing authorization for any indication in any country. MEDI4736 is currently under investigation in ten clinical trials either as monotherapy or as combination therapy for advanced stage solid tumors. According to the Swiss Human Research Act (HRA) and its corresponding ordinance KlinV/Oclin on clinical trials, this trial is classified as category C.

OBJECTIVE(S)

Trial objective(s):

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 MEDI4736) to standard chemotherapy (with cisplatin/docetaxel) in primary resectable stage IIIA(N2) NSCLC is efficacious and feasible.

ENDPOINTS

Primary endpoint:

- Event-free survival (EFS) at 12 months

  An event is defined as relapse or progression according to RECIST 1.1 criteria, secondary tumor or death due to any cause.

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:

Patient participation is mandatory

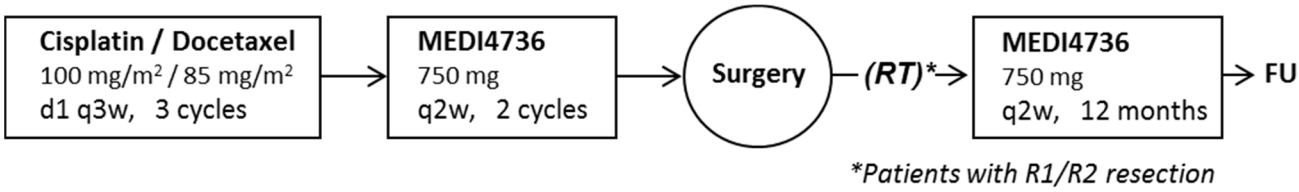
- Comparison of the tumor immunome at the time of diagnosis (treatment-naive) and at the time of tumor resection (after neoadjuvant chemo- and immunotherapy)
- Investigation of efficacy outcome parameters (EFS, OR, OS) in relation to tissue expression of PD-L1 (tumor and immune cells)
- Investigation of biomarkers for anti-PD-L1 treatment and their relation to efficacy outcome parameters of interest (EFS, OS and OR after neoadjuvant immunotherapy)

Patient participation is optional

- Investigation of the effect of the intestinal microbiota on the response to immunotherapy

TRIAL DESIGN

Multicenter, single-arm, phase II trial



SELECTION OF PATIENTS

Refer to section 6 for the full list of inclusion/exclusion criteria

- Pathologically proven NSCLC (adeno-, squamous-, large cell carcinoma or NSCLC not otherwise specified) irrespective of genomic aberrations or PD-L1 expression status.
- Tumor tissue is available for the mandatory translational research (preferably histology, cytology allowed).
- Tumor stage T1-3N2M0 (stage IIIA(N2) according to the 7th edition of the TNM classification; October 2009).
- Tumor is considered resectable based on a multidisciplinary tumor board decision made before neoadjuvant treatment.
- Age 18-75 years.
- WHO performance status 0-1.
- Adequate lung, cardiac, hepatic and renal functions.
- Adequate hematological values.
- No previous or concomitant malignancy within 5 years prior registration (see exceptions).
- No previous therapy for NSCLC; no previous treatment with a PD-1 or PD-L1 inhibitor; no previous radiotherapy to the chest.
- No preexisting peripheral neuropathy.
- No active autoimmune disease requiring systemic treatment within the past 3 months; no documented history of clinically severe autoimmune disease (see exceptions).
- No history of primary immunodeficiency, allogeneic organ transplant or previous clinical diagnosis of tuberculosis; no known evidence of acute or chronic hepatitis B, hepatitis C or human immunodeficiency virus (HIV) infection.

INVESTIGATIONAL MEDICINAL PRODUCT

For this trial MEDI4736 (durvalumab) is the IMP.

MEDI4736 is a human monoclonal antibody (mAb) of the immunoglobulin (Ig)G1 kappa subclass against PD-L1.

TRIAL TREATMENT

The trial investigates the addition of pre- and post-operative immune checkpoint inhibition with the anti-PD-L1 antibody MEDI4736 to the previously established standard of care for stage IIIA(N2) patients, which is based on the trials SAKK16/96 and SAKK16/00. Patients whose tumor is deemed resectable at diagnosis will receive 3 cycles (21 days each) of standard chemotherapy with cisplatin/docetaxel followed by 2 cycles (14 days each) of neoadjuvant immunotherapy with MEDI4736 750 mg. Following surgery, patients with complete resection (R0) of their tumor will be administered adjuvant treatment with MEDI4736 750 mg for up to one year or until recurrence, death, unacceptable toxicity or consent withdrawal (whichever occurs first). Patients with incomplete R1/R2 resection, including patients with extracapsular spread of mediastinal lymph node metastases, may undergo standard radiotherapy prior to adjuvant treatment with MEDI4736.

MEASUREMENTS AND PROCEDURES

Baseline assessments before trial therapy comprise a positron emission tomography/computed tomography (PET/CT) with contrast enhanced CT scan of thorax and upper abdomen, a brain magnetic resonance imaging (MRI) or CT, echocardiography and electrocardiogram (ECG), pulmonary function tests, physical examination and blood and urine testing for safety parameters (hepatic, renal, metabolic and thyroid function, hematology). A pregnancy test for women in child-bearing age will also be performed.

During neoadjuvant chemotherapy, regular physical examination and blood testing for safety parameters (hepatic, renal, metabolic function, hematology) will be performed. A PET/CT with contrast enhanced CT scan of thorax and upper abdomen is to be done at the end of the last (third) cycle of chemotherapy.

Prior to neoadjuvant treatment with MEDI4736, patients will undergo an ECG and thyroid function analysis, as well as blood and urine testing for safety parameters (hepatic, renal, metabolic function, hematology). During the course of the treatment, regular physical examination and blood testing for safety parameters will be performed. Besides, vital signs will be monitored during each infusion of MEDI4736 and also post-infusion for the first cycle of treatment.

Assessments prior to surgery comprise a PET/CT with contrast enhanced CT scan of thorax and upper abdomen, ECG or echocardiography, pulmonary function tests, physical examination and blood testing for safety parameters (hepatic, renal, metabolic, thyroid function, hematology and coagulation factors). In case post-surgery radiotherapy is administered, patients will be assessed for AEs during the course of the radiation therapy.

During adjuvant immunotherapy until and including at the end of the treatment, physical examinations and laboratory investigations for safety parameters (hepatic, renal, metabolic and thyroid function, hematology) will take place at regular intervals. An ECG is to be performed at cycle 1, cycle 9 and at the end of treatment. Contrast enhanced CT scans of thorax and upper abdomen will be performed 1 month after surgery and every 3 months thereafter.

In addition, tumor material (histology preferred, cytology accepted) will be collected prior to the start of trial therapy and a resected tumor specimen will be collected at surgery. Peripheral blood will be collected at baseline, prior to the start of neoadjuvant MEDI4736 therapy, prior to surgery, prior to the 5^{th} application of adjuvant MEDI4736 therapy and at the end of trial treatment (whether completed as per protocol or prematurely discontinued due to recurrence or any of the listed events). Stool samples at baseline and during aduvant MEDI4736 therapy will be collected from patients who consent to give such a sample. A tumor biopsy or cytology specimen may be optionally collected at recurrence.

The patients will be followed up lifelong. Visits, involving physical examination and contrast enhanced thorax CT scan alternating with chest X-ray will take place every 3 months for 2 years after the end of trial therapy, every 6 months during the years 3 to 5 and once a year thereafter. The frequency of follow-up visits and of medical assessments is in line with the international guidelines for the diagnosis and treatment of locally advanced NCSLC.

NUMBER OF PARTICIPANTS

It is planned to include 68 patients in ca. 20 participating sites.

TRIAL DURATION

Duration of accrual: 3 years

Duration of trial therapy (per patient): 16 to 18 months

Duration of follow-up (per patient): lifelong

Duration of trial in total: unknown (*lifelong follow-up*)

The trial may be stopped early based on the results of an interim safety analysis or if new scientific data become available which change the assessment of risk/benefit.

TRIAL SCHEDULE

First patient in: Q1 2016 (planned)

Last patient in: Q1 2019 (planned)

End of trial therapy: Q3 2020 (planned)

Last patient, last visit: unknown (*lifelong follow-up*)

STATISTICAL CONSIDERATIONS

The sample size is based on the EFS at 12 months after registration. A rate ≤ 48% of EFS at 12 months after registration 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 due to non-compliance to the criteria for the full analysis set (FAS; see section 13), the target sample size is increased to 68 patients.

GCP STATEMENT

This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by the International Conference on Harmonization (ICH), as well as national legal and regulatory requirements.

2 INTRODUCTION AND BACKGROUND

2.1 Disease background

Lung cancer is the most common cancer both in incidence and in mortality globally with 1.35 million deaths annually [1]. In Europe lung cancer is predicted to cause nearly 280'000 deaths (both sexes combined) in 2015, corresponding to over 20% of total cancer deaths [2]. In Switzerland 3'700 patients are diagnosed yearly with lung cancer [3].

Non-small cell lung cancer (NSCLC) accounts for more than 80% of all lung cancers. Overall, the 5 year survival rate in NSCLC is about 14% and mainly depends on the stage at diagnosis [4]. About one fourth of patients with NSCLC initially present with locally advanced stage III disease [5].

Locally advanced disease has traditionally been one of the major challenges due to its broad heterogeneity and, most importantly, a possibility for cure in selected subgroups of the patients. Historically, stage III NSCLC was defined as loco-regionally advanced disease with extra-pulmonary invasion into surrounding organs (T3/T4) and/or malignant involvement of ipsilateral (N2) or contralateral (N3) lymph nodes but no evidence of distant metastasis. Stage IIIA includes T1-3 tumors with mediastinal lymph node involvement (N2), T3 tumors with ipsilateral hilar (N1) or mediastinal (N2) lymph node involvement and T4 tumors in the absence of nodal metastases (N0) or with hilar lymph node metastases (N1) [6]. From a therapeutic point of view patients with locally advanced NSCLC are divided into a subgroup deemed potentially resectable at disease diagnosis and a group of patients with disease deemed non-resectable.

2.2 Therapy background

Stage IIIA(N2) is deemed resectable if a complete tumor resection may be achieved. Resectability is determined irrespective of any pre-operative treatment. Evaluation of resectability includes radiographic imaging techniques (computed tomography (CT), positron emission tomography–computed tomography (PET/CT) or magnetic resonance imaging (MRI)) and, in case of centrally located tumors, more invasive staging procedures as video-mediastinoscopy in order to exclude a more advanced stage disease (e.g. infiltration of the contralateral main bronchus). The suspicion of an involvement of several mediastinal lymph nodes or mediastinal lymph node stations is not an exclusion criterion if the thoracic surgeon assesses the mediastinal lymph nodes as resectable.

Role of pre- or post-operative chemotherapy

Many phase II trials demonstrated the safety and efficacy of preoperative chemotherapy [7-11]. Randomized trials suggested an additional benefit when neoadjuvant chemotherapy was added to surgery [12-15]. The results were consistently in favor of primary chemotherapy prior surgery compared to surgery alone. However, these trials enrolled small number of patients and the differences in outcome were not statistically significant in most cases.

A recently updated Cochrane meta-analysis (evaluating 11,107 patients in 47 trials) reported a clear benefit of the addition of platinum-based chemotherapy, either as adjuvant or neoadjuvant, over surgery alone in stage IB-III [16]. In particular, the meta-analysis showed that among the 35 trials (8447 enrolled patients) which evaluated surgery plus adjuvant chemotherapy versus surgery alone, the addition of chemotherapy to surgery resulted in an absolute increase in survival of 4% at five years (HR 0.86, 95% CI 0.81-0.92, p<0.0001).

Another meta-analysis, using data from 16 trials with 3728 patients, evaluated the role of pre-operative chemotherapy in comparison to surgery alone for resectable NSCLC [17]. The pooled hazard ratio for overall survival was 0.84 (95% CI 0.77-0.91, p<0.001). Seven of these trials (1447 patients) were limited to stage III disease. The pooled HR for these 7 trials was 0.77 (95% CI 0.68-0.87, p<0.001).

Hence, neoadjuvant or adjuvant chemotherapy for stage IIIA NSCLC is now considered standard of care. Encouragingly, preoperative chemotherapy appears to be better tolerated than adjuvant chemotherapy, with a high compliance of 90-95% [15, 18].

In the three-arm NATCH trial from the Spanish Lung Cancer Group, 624 patients with stages IA-II were randomly assigned to receive induction chemotherapy with carboplatin/paclitaxel followed by surgery or surgery followed by adjuvant chemotherapy or surgery alone [19]. Although the majority of patients had stage IA disease there was a non-significant trend for improved 5-year disease-free survival rates with neoadjuvant chemotherapy. In the subgroup of stage II (T3N1) patients disease-free survival rates favored the neoadjuvant arm. A significantly greater proportion (90%) of patients in the neoadjuvant group received the planned three cycles of neoadjuvant chemotherapy compared with the adjuvant group (66%).

Role of surgery

A second question for stage IIIA disease is whether surgery leads to a better prognosis compared to definitive combined chemo-radiotherapy. Several randomized trials investigated the role of surgery with slightly different trial design. Postoperative morbidity and mortality is an important issue in this setting. In the RTOG 89-01 trial surgery did not increase the mortality rate [20]. The EORTC trial [21] and the US Intergroup trial [22] showed an increased morbidity and mortality rate for patients undergoing pneumonectomy compared to more limited surgical approaches (lobectomy, bilobectomy). An exploratory matching analysis of the US Intergroup trial showed a benefit of the addition of surgery if pneumonectomy is avoided. In the SAKK trials, the perioperative mortality was 0-3% [23, 24].

In summary, these trials showed that surgery after neoadjuvant therapy is feasible in selected patients with N2 disease at experienced centers with recorded low perioperative mortality and results in median and 5 years overall survival which were comparable to those obtained after definitive chemo-radiotherapy (Table 1).

Table 1. Randomized phase III studies comparing neoadjuvant therapy and surgery to definitive chemo-radiotherapy.

Study (year)	N	Induction therapy/Surgery	Chemo-Radiotherapy (CRT)	Median OS (months)		5-year OS (%)		Log-rank test p-value
				Induction	CRT	Induction	CRT	
Johnstone (2002) [20]	45	Cis/Vinblastine	Chemo → RT	19.4	17.4	22*	22*	0.46
Van Meerbeeck (2007) [21]	332	Platinum-based	Chemo → RT	16.4	17.5	15.7	14	0.60
Albain (2009) [22]	396	Cis/Eto/RT (45 Gy)	Cis/Eto/RT (61 Gy)	23.6	22.2	27	20	0.24

* at 4 years

Cisplatin/Docetaxel as chemotherapy backbone

Docetaxel has been extensively tested in the metastatic setting in patients with NSCLC as monotherapy [25] or in combination with cisplatin [26, 27] and other agents [28, 29], either in first-line or in second-line treatment after failure of a cisplatin-based chemotherapy [30, 31]. The combination of cisplatin with docetaxel can be considered one of the standard regimens for the therapy of stage IV NSCLC based on the four-arm ECOG trial [32]. One randomized trial investigated the role of single agent docetaxel in stage III NSCLC, either as induction therapy before radiotherapy or as neoadjuvant treatment [33]. The control arm was local therapy alone. There was a trend towards a favorable survival in the docetaxel arm.

Previous SAKK trials for stage IIIA(N2) NSCLC

The SAKK substantially contributed to establish a standard of care for patients with locally advanced stage III NSCLC. In the single-arm phase II trial SAKK 16/96, 90 patients with stage IIIA(N2) NSCLC were treated with three cycles of neoadjuvant chemotherapy using cisplatin and docetaxel followed by surgery [18]. Postoperative radiotherapy was offered to patients with involvement of the first mediastinal lymph nodes or with positive resection margins. The overall response rate was 66%. With surgery alone the 5-year overall survival in this group of patients is 9% for T3N1 disease, respectively 13% for T1-3N2 disease [34]. This rate was improved by the addition of neoadjuvant chemotherapy with a median overall survival of 35 months and a cure rate

(survival without evidence of disease) after 3 years of 36% [23]. Eighty-seven percent of patients underwent surgery. Radical resection of the residual tumor was possible in 84%, complete resection was possible in 57% of the operated patients. The median duration of remission was 15 months. Several clinical and pathological assessments (clinical response, pathological response, mediastinal down-staging) as well as complete resection were significantly associated with improved prognosis.

The addition of radiotherapy as a third treatment modality to neoadjuvant chemotherapy and surgery was investigated in the trial SAKK 16/00 [35]. Patients randomized into the chemotherapy-alone arm received three cycles of cisplatin/docetaxel whereas patients allocated to the combined therapy arm received the same chemotherapy regimen, followed by accelerated concomitant boost of 44 Gy in 22 fractions within 3 weeks. There was no difference in local failure, event-free survival or OS between the two arms.

In total, more than 400 patients with stage IIIA NSCLC were treated within the previous SAKK trials. Based on the results of these trials, induction chemotherapy with cisplatin and docetaxel for three cycles followed by tumor resection is now an accepted standard of care. However, with a 12-month EFS of 48% only, based on the SAKK experience, the addition of new therapeutic approaches is necessary to improve outcomes for patients with advanced, resectable NSCLC.

2.3 Cancer immunotherapy

Cancer immunotherapy is attracting increasing attention following recent outstanding results of immunotherapeutic approaches in various metastatic solid tumors [36-38]. Based on these promising results and the development of new molecules unleashing the immune system, immunotherapy has again raised interest in the treatment of lung cancer after controversial results from early clinical immunotherapy trials.

Immune checkpoint inhibitors have so far only been investigated in advanced/metastatic lung cancer and mainly in pre-treated patients. The activity of the antibody against cytotoxic T-lymphocyte-associated protein (CTLA)-4 ipilimumab (10 mg/kg) in combination with paclitaxel and carboplatin was evaluated in a randomized phase II trial in patients with chemotherapy-naïve stage IIIB(IV) NSCLC [39]. The immune-related progression free survival (ir-PFS) as primary endpoint was significantly prolonged in patients receiving a phased schedule of ipilimumab versus chemotherapy alone (median ir-PFS 5.7 vs. 4.6 months, HR 0.72, p=0.05). Combining ipilimumab with paclitaxel and carboplatin did not increase overall treatment-related toxicities.

In a phase I trial the anti-programmed cell death protein (PD)-1 antibody nivolumab was administered in monotherapy to patients with various solid tumors, including 129 patients with NSCLC [40, 41]. In NSCLC patients, objective responses were observed across doses of 1-10 mg/kg and in all histological subtypes. With extended treatment, the median response duration for the 3 mg/kg dose had not been reached at the time of analysis (range, 16.1+ to 133.9+ weeks). The phase II trial CheckMate 063 investigated nivolumab in patients with metastatic squamous cell carcinoma of the lung previously treated with two or more lines of palliative chemotherapy [42]. The objective response rate was 14.5%, whereas 26% of patients showed disease stabilization. 77% of patients with an objective response showed ongoing response at the time of analysis. The median duration of response was not reached at the time of data analysis. Median OS in this heavily pretreated population was 8.2 months with 40.8% of patients living longer than 12 months. CheckMate 017 randomized patients to either second-line chemotherapy with docetaxel or nivolumab. Median OS was significantly improved with nivolumab (9.2 vs. 6.0 months, HR 0.59, 95%CI 0.44-0.79, p=0.00025) [43]. The CheckMate 057 trial asked the same question in patients with metastatic lung adenocarcinoma. The trial was recently unblinded based on a planned interim analysis showing superiority for the primary endpoint overall survival [44].

In the KEYNOTE-001 trial 495 stage IV NSCLC patients with programmed cell death ligand (PD-L)1 expression were randomized between two schedules of the anti-PD-1 antibody pembrolizumab (10 mg/kg every two or every three weeks) [45]. The ORR was 19.4%. The median duration of response was 12.5 months with a median progression-free survival of 3.7 months and a median OS of 12.0 months.

The first results from the OAK trial, a randomized phase III trial with the anti-PD-L1 inhibitor atezolizumab in second-line therapy for NSCLC, have been reported very recently. In this trial,

1225 patients after failure of at least one platinum-based therapy were randomized between docetaxel and atezolizumab. OS was improved by 4.2 months with atezolizumab (9.6 vs. 13.8 months, HR 0.73, p=0.0003) [46].

2.4 Novel investigational product

MEDI4736 is a human monoclonal antibody (mAb) of the immunoglobulin (Ig)G1 kappa subclass that inhibits binding of PD-L1 [B7 homolog 1 (B7-H1), cluster of differentiation (CD)274] to PD-1 [CD279] and B7-1 [CD80] [47]. MEDI4736 is composed of two identical heavy chains and two identical light chains, with an overall molecular weight of approximately 149 kDa. MEDI4736 contains a triple mutation in the constant domain of the IgG1 heavy chain that reduces binding to complement protein C1q and the Fcγ receptors involved in triggering effector function [48].

PD-1 is an extracellular protein that down-regulates immune responses primarily in peripheral tissues through binding to its two ligands PD-L1 and PD-L2. As inhibitory receptor expressed on T cells following T-cell activation, PD-1 sustains, at least in part, a T cell dysfunctional state upon chronic stimulation such as chronic infection or cancer [49, 50]. Binding of PD-L1 with PD-1 inhibits T-cell proliferation, cytokine production, and cytolytic activity, leading to functional inactivation of T cells. The latter is commonly referred to as T cell exhaustion. B7.1 is a molecule expressed on antigen-presenting cells and activated T cells. In contrast to the interaction of CD28/B7.1, PD-L1 binding to B7.1 on T cells mediates inhibition of T-cell activation and cytokine production [50, 51].

Overexpression of PD-L1 on tumor cells has been reported to impede antitumor immunity, resulting in immune evasion [52]. Therefore, interruption of the PD-L1/PD-1 pathway represents an attractive strategy to restore tumor-specific T-cell immunity. PD-L1 expression is prevalent in many human tumors. PD-L1 expression can be found in up to 50% of patients with NSCLC and is associated with a poor prognosis [53]. However, the role of PD-L1 expression has not been clearly defined as PD-L1 is not only expressed on tumor cells but also on infiltrating immune cells

2.4.1 Preclinical data

The non-clinical experience is fully described in the current version of the Investigator's Brochure (IB) [47].

MEDI4736 antagonizes the inhibitory effect of PD-L1 by blocking PD-L1 binding to PD-1 on human T cells. This results in the recovery of T cell effector functions such as cellular proliferation and release of interferon (IFN)-γ. In vivo studies showed that MEDI4736 inhibits tumor growth in a xenograft model via a T-cell dependent mechanism. Moreover, an anti-mouse PD-L1 antibody lead to improved survival in a syngeneic tumor model when given as monotherapy and resulted in complete tumor regression in >50% of treated mice when given in combination with chemotherapy.

2.4.2 Pharmacokinetics and pharmacodynamics

Clinical data is fully described in the current version of the IB [47].

The pharmacokinetics (PK) and immunogenicity profiles of MEDI4736 as monotherapy are described below based on data from key studies.

As of February 9th 2015, PK data were available for 378 patients in the dose-escalation and dose-expansion phases of Study CD-ON-MEDI4736-1108 following treatment with MEDI4736 0.1 to 10 mg/kg every 2 weeks (q2w) or 15 mg/kg every 3 weeks (q3w). The maximum observed concentration (C_{max}) increased in an approximately dose-proportional manner over the dose range of 0.1 to 15 mg/kg. The area under the concentration-time curve from 0 to 14 days (AUC0-14) increased in a greater than dose-proportional manner over the dose range of 0.1 to 3 mg/kg and increased dose-proportionally at ≥ 3 mg/kg. These results suggest that MEDI4736 exhibits nonlinear PK likely due to saturable target-mediated clearance at doses < 3 mg/kg and approaches linearity at doses ≥ 3 mg/kg. Near complete target saturation (soluble PD-L1 and membrane bound) is expected with MEDI4736 ≥ 3 mg/kg q2w. Exposures after multiple doses showed accumulation consistent with the PK parameters estimated from the first dose. In addition, simulations indicated that following MEDI4736 10 mg/kg q2w dosing, >90% of patients are expected to maintain PK exposure ≥ 40 µg/ml throughout the dosing interval.

As of February 9th 2015, a total of 388 patients provided samples for anti-drug antibodies (ADA) analysis. Only 8 of 388 patients (1 subject each in 0.1, 1, 3, and 15 mg/kg cohorts, and 4 subjects in 10 mg/kg cohort) were ADA-positive with an impact on PK/pharmacodynamics in 1 subject in the 3 mg/kg cohort.

2.4.3 Safety

The safety profile of MEDI4736 as monotherapy and combined with other anticancer agents is consistent with the pharmacology of the target and other agents in the immune checkpoint inhibitor class. No tumor types appeared to be associated with unique AEs. Immune-related AEs, which are important risks of immune checkpoint inhibitors, have been observed with MEDI4736 and include colitis, pneumonitis, hepatitis/hepatotoxicity, neuropathy/neuromuscular toxicity, endocrinopathy, dermatitis, and nephritis [47]. These events are manageable by available/established treatment guidelines as described in the present protocol.

Adverse event profile of MEDI4736 monotherapy

The safety profile of MEDI4736 monotherapy in the 694 patients with advanced solid tumors treated at 10 mg/kg q2w in Study CD-ON-MEDI4736-1108 has been broadly consistent with that of the overall 1,279 patients who have received MEDI4736 monotherapy (not including patients treated with blinded investigational product) across the clinical development program. The majority of treatment-related AEs was 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 toxicity. As of May 7th 2015, among the 694 patients treated with MEDI4736 10 mg/kg q2w in this study, a total of 378 patients (54.5%) experienced a treatment-related AE, with the most frequent (occurring in ≥ 5% of patients) being fatigue (17.7%), nausea (8.6%), diarrhea (7.3%), decreased appetite (6.8%), pruritus (6.3%), rash (6.1%), and vomiting (5.0%). A majority of the treatment-related AEs were Grade 1 or Grade 2 in severity with ≥ Grade 3 events occurring in 65 patients (9.4%). Treatment-related ≥ Grade 3 events reported in 3 or more patients (≥ 0.4%) were fatigue (12 patients, 1.7%); increased aspartate aminotransferase (AST; 7 patients, 1.0%); increased gamma-glutamyltransferase (GGT; 6 patients, 0.9%); increased alanine aminotransferase (ALT; 5 patients, 0.7%); and colitis, vomiting, decreased appetite, and hyponatremia (3 patients, 0.4% each). Six patients had treatment-related Grade 4 AEs (upper gastrointestinal hemorrhage, increased AST, dyspnea, neutropenia, colitis, diarrhea, and pneumonitis) and 1 subject had a treatment-related Grade 5 event (pneumonia). Treatment-related serious adverse events (SAEs) that occurred in ≥ 2 patients were colitis and pneumonitis (3 patients each). A majority of the treatment-related SAEs were ≥ Grade 3 in severity and resolved with or without sequelae. AEs that resulted in permanent discontinuation of MEDI4736 were considered as treatment related in 18 patients (2.6%), with colitis being the most frequent treatment-related AE resulting in discontinuation (3 patients). A majority of the treatment-related AEs resulting in discontinuation of MEDI4736 were ≥ Grade 3 in severity and resolved with or without sequelae.

The safety profile of MEDI4736 monotherapy in Study CD-ON-MEDI4736-1108 is generally consistent with that of Study D4191C00003/ATLANTIC in patients with locally advanced or metastatic NSCLC treated with MEDI4736 10 mg/kg q2w. As of May 5th 2015, 264 of 303 patients (87.1%) reported any AE in this study. Overall, events reported in ≥ 10% of patients were dyspnea (18.8%), fatigue (17.8%), decreased appetite (17.5%), cough (14.2%), pyrexia (12.2%), asthenia (11.9%), and nausea (11.2%). Nearly two-thirds of the patients experienced AEs that were Grade 1 or 2 in severity and manageable by general treatment guidelines as described in the current protocol. Grade 3 or higher AEs were reported in 107 of 303 patients (35.3%). A total of 128 patients (42.2%) reported AEs that were considered by the investigator as related to MEDI4736. Treatment-related AEs (all grades) reported in ≥ 2% of patients were decreased appetite (6.6%); fatigue (5.9%); asthenia (5.0%); nausea (4.6%); pruritus (4.3%); diarrhea, hyperthyroidism, hypothyroidism, and pyrexia (3.3% each); rash (2.6%); weight decreased (2.3%); and vomiting (2.0%). Treatment-related Grade 3 AEs reported in ≥ 2 patients were pneumonitis (3 patients) and increased GGT (2 patients). There was no treatment-related Grade 4 or 5 AEs. Ninety-four of 303 patients (31.0%) reported any SAE. SAEs that occurred in ≥ 1.0% of patients were dyspnea (6.6%); pleural effusion, general physical health deterioration (2.3% each); pneumonia (2.0%); hemoptysis, pulmonary embolism (1.3% each); and pneumonitis, respiratory failure, disease

progression (1.0% each). Nine patients had an SAE considered by the investigator as related to MEDI4736. Each treatment-related SAE occurred in 1 subject each with the exception of pneumonitis, which occurred in 3 patients. Fifteen of 303 patients (5.0%) have died due to an AE (pneumonia (3 patients); general physical health deterioration, disease progression, hemoptysis, dyspnea (2 patients each); pulmonary sepsis, respiratory distress, cardiopulmonary arrest [verbatim term (VT)], hepatic failure, and sepsis (1 subject each). None of these events was considered related to MEDI4736. Twenty-three of 303 patients (7.6%) permanently discontinued MEDI4736 treatment due to AEs. Events that led to discontinuation of MEDI4736 in ≥ 2 patients were dyspnea, general physical health deterioration, and pneumonia. Treatment-related AEs that led to discontinuation were increased ALT and increased hepatic enzyme, which occurred in 1 subject each.

2.4.4 Clinical data

As of the data cut-off dates (15 April 2015 to 12 July 2015), a total of 1'883 patients have been enrolled and treated in 30 ongoing clinical studies with MEDI4736, including 20 sponsored (Table 2) and 10 collaborative studies. Of the 1'883 patients, 1'279 received MEDI4736 monotherapy, 440 received MEDI4736 in combination with tremelimumab or other anticancer drugs. Fourteen received other agents (gefitinib, MEDI6383), and 150 have been treated with blinded investigational product. No studies have been completed so far nor has one of the trials been terminated prematurely due to toxicity.

Table 2. Overview of ongoing sponsored clinical trials with MEDI4736, as of July 2015. A comprehensive list on ongoing sponsored and collaborative MEDI4736 studies can be found in the current version of the IB.

Study Number	Phase	Study Population	Treatment Regimen	Patients Treated
Sponsored MEDI4736 Monotherapy Studies (N=1'149)				
CD-ON-MEDI4736-1108 (NCT01693562)	I/II	Advanced solid tumors	MEDI4736 q2w or q3w	736
D4190C00002 (NCT01938612)	I	Advanced solid tumors (Japan)	MEDI4736 q2w or q3w	70
D4190C00007 (NCT02117219)	I	MDS	MEDI4736 q2w	32
D4193C00001 (HAWK) (NCT02207530)	II	Recurrent/metastatic PD-L1+ SCCHN	MEDI4736 q2w	8
D4190C00003 (ATLANTIC) (NCT02087423)	II	Locally advanced/metastatic PD-L1+ NSCLC (stage IIIB/IV)	MEDI4736 q2w	303
D4190C00001 (PACIFIC) (NCT02125461)	III	Locally advanced, unresectable NSCLC (stage III)	MEDI4736 q2w or placebo	115 [1]
Sponsored MEDI4736 Combination or Sequential Therapy Studies (N=350)				
D-ON-MEDI4736-1161 (NCT02027961)	I	Metastatic or unresectable melanoma	MEDI4736 q2w + trametinib ± dabrafenib	65
D791PC00001 (NCT02088112)	I	Locally advanced/metastatic NSCLC	MEDI4736 q2w + gefitinib	33 [2]
D6020C00001 (NCT02118337)	I	Advanced malignancies	MEDI4736 q2w + MEDI0680 (AMP-514) q2w or q4w	21
D4880C00010 (NCT02141347)	I	Advanced solid malignancies (Japan)	MEDI4736 q2w + Tremelimumab	10
D4190C00010 (NCT02261220)	I	Advanced solid tumors	MEDI4736 q2w + Tremelimumab	51
D4190C00011 (NCT02262741)	I	Recurrent/metastatic SCCHN	MEDI4736 q2w + Tremelimumab	13
D6050C00001 (NCT02221960)	I	Advanced solid tumors	MEDI6383 alone and in combination With MEDI4736	13 [3]

D4190C00006 (NCT02000947)	IB	Advanced NSCLC	MEDI4736 q2w + Tremelimumab	102
D5160C00006 (TATTON) (NCT02143466)	IB	EGFRm+ advanced NSCLC	AZD9291 in combination with MEDI4736	23
D4190C00021 (NCT02340975)	IB/II	Metastatic/recurrent gastric or GEJ adenocarcinoma	MEDI4736 with Tremelimumab, MEDI4736 or Tremelimumab monotherapy	1
D4981C00001 (NCT02205333)	IB/II	Advanced solid tumors or aggressive B-cell lymphomas	MEDI6469 in combination with MEDI4736	13
D4193C00003 (CONDOR) (NCT02319044)	II	Recurrent/metastatic PD-L1- SCCHN	MEDI4736 monotherapy, tremelimumab monotherapy, and MEDI4736 + tremelimumab combination therapy	8 [1]
D4191C00011 (NCT02179671)	IIA	Locally advanced/metastatic NSCLC	Selected small molecules (Gefitinib, AZD9291, or Selumetinib + Docetaxel) or a 1st immune-mediated therapy (Tremelimumab) with a sequential switch to a 2nd immune-mediate therapy (MEDI4736)	19
D4191C00004 (ARCTIC) (NCT02352948)	III	Locally advanced/metastatic NSCLC (stage IIIB-IV)	MEDI4736, given as monotherapy or in combination with Tremelimumab determined by PD-L1 expression versus standard of care	27 [1]

MDS: myelodysplastic syndrome; q2w: every 2 weeks; q3w: every 3 weeks; q4w: every 4 weeks; CRT: chemo-radiotherapy.

[1] patients received blinded investigational product
[2] one of the 33 patients received gefitinib only
[3] all 13 patients received MEDI6383 monotherapy

Partial efficacy data are available for two monotherapy trials (CD-ON-MEDI4736-1108 and D4190C00007) and two combination therapy studies (CD-ONMEDI47361161 and D4190C00006). Clinical activity has been observed in all four studies.

Study CD-ON-MEDI4736-1108

Overall, 456 of 694 patients treated with MEDI4736 10 mg/kg q2w were evaluable for response (defined as having ≥ 24 weeks follow-up, measurable disease at baseline, and ≥ 1 follow-up scan, or discontinued due to disease progression or death without any follow-up scan) In PD-L1 unselected patients, the objective response rate (ORR), based on investigator assessment per RECIST v1.1, ranged from 0% in uveal melanoma (n=23) to 20% in bladder cancer (n=15), and disease control rate at 24 weeks ranged from 4.2% in triple-negative breast cancer (TNBC; n=24) to 39.1% in advanced cutaneous melanoma (n=23). PD-L1 status was known for 383 of the 456 response evaluable patients. Across the PD-L1-positive tumors, ORR was highest for bladder cancer, advanced cutaneous melanoma, hepatocellular carcinoma (HCC; n=3 each, 33.3% each), NSCLC (n=86; 26.7%), and squamous cell carcinoma of the head and neck (SCCHN; n=22, 18.2%). In the PD-L1-positive subset, disease control rate at 24 weeks was highest in advanced cutaneous melanoma (n=3; 66.7%), NSCLC (n=86; 36%), HCC and bladder cancer (n=3 each; 33.3% each), and SCCHN (n=22; 18.2%).

Study D4190C00007

Of the 32 patients with myelodysplastic syndrome (MDS) treated in this trial, 21 patients had at least 1 post-baseline disease assessment. Among these patients, the best overall responses were

marrow complete remission in 4 patients (19%); stable disease in 4 patients (19%); and progressive disease in 5 patients (23.8%). The remaining 8 patients (38.1%) did not meet the criteria for complete remission, marrow complete remission, partial remission, stable disease, or progressive disease at the date of assessment.

Study CD-ON-MEDI4736-1161

Of the 65 patients with metastatic or unresectable melanoma treated with the combination of MEDI4736 and BRAF inhibitor (BRAFi; dabrafenib)/MEK inhibitor (MEKi; trametinib), 63 patients were evaluable for response. A total of 35 patients (55.6%) had a best overall response of confirmed or unconfirmed PR The disease control rate (CR + PR + SD ≥ 12 weeks) was 79.4%.

Study D4190C00006

This study is a multicenter, non-randomized, open-label, phase Ib study enrolling immunotherapy-naïve patients with metastatic NSCLC [54]. Patients were treated with MEDI4736 in doses of 3 mg/kg, 10 mg/kg, 15 mg/kg, or 20 mg/kg every 4 weeks, or 10 mg/kg every 2 weeks, and tremelimumab in doses of 1 mg/kg, 3 mg/kg, or 10 mg/kg every 4 weeks for six doses then every 12 weeks for three doses. Between Oct 28, 2013, and Apr 1, 2015, 102 patients were enrolled into the dose-escalation phase and received treatment. The maximum tolerated dose was exceeded in the cohort receiving MEDI4736 20 mg/kg every 4 weeks plus tremelimumab 3 mg/kg, with two (30%) of six patients having a dose-limiting toxicity (one G3 increased aspartate aminotransferase and alanine aminotransferase and one G4 increased lipase). The most frequent treatment-related G3 and G4 AEs were diarrhea (eleven [11%]), colitis (nine [9%]), and increased lipase (eight [8%]). Discontinuations attributable to treatment-related AEs occurred in 29 (28%) of 102 patients. Treatment-related serious AEs occurred in 37 (36%) of 102 patients. 22 patients died during the study, and three deaths were related to treatment. The treatment-related deaths were due to complications arising from myasthenia gravis (MEDI4736 10 mg/kg every 4 weeks plus tremelimumab 1 mg/kg), pericardial effusion (MEDI4736 20 mg/kg every 4 weeks plus tremelimumab 1 mg/kg), and neuromuscular disorder (MEDI4736 20 mg/kg every 4 weeks plus tremelimumab 3 mg/kg). Evidence of clinical activity was noted both in patients with PD-L1-positive tumors and in those with PD-L1-negative tumors. Investigator-reported confirmed objective responses were achieved by six (23%, 95% CI 9-44) of 26 patients in the combined tremelimumab 1 mg/kg cohort, comprising two (22%, 95% CI 3-60) of nine patients with PD-L1-positive tumors and four (29%, 95% CI 8-58) of 14 patients with PD-L1-negative tumors, including those with no PD-L1 staining (four [40%, 95% CI 12-74] of ten patients).

Study D5160C00006 (TATTON)

TATTON is a trial investigating the combination of MEDI4736 with the third generation EGFR tyrosine kinase inhibitor osimertinib in EGFR mutation-positive NSCLC [55]. In this phase I trial, patients received osimertinib 80 mg QD plus MEDI4732 3 mg/kg bi-weekly or osimertinib 80 mg QD plus MEDI4736 10 mg/kg bi-weekly. The latter dose was chosen for the dose expansion cohort. The trial was halted after an increase in interstitial lung disease (ILD) has been reported with the combinatioin of osimertinib and MEDI4736 compared to what would be expected with either drug alone. ILD was reported in 13 out of 34 patients (38%). Five events were G3/4. In patients with prior EGFR-tyrosine kinase inhibitor therapy, investigator-assessed ORR was 67% (6/9) and 21% (3/14) in those with T790M positive and T790M negative NSCLC, respectively, and 70% (7/10) in EGFRm treatment-naïve patients.

2.4.5 Potential biomarkers

This trial provides the unique opportunity for a comprehensive translational research program through the collection of tumor tissue from treatment-naïve patients, tumor resection specimens after neoadjuvant therapy and re-biopsies at the time of tumor progression during immunotherapy.

There are conflicting results concerning the predictive value of PD-L1 expression for anti-PD-L1 antibody therapy. Emerging data suggest that patients whose tumors show PD-L1 expression by immunohistochemistry derive more benefit from anti-PD-L1 directed treatment, but the presence of tumor responses in patients with low levels or even lack of expression of PD-L1 challenge the role of PD-L1 expression as an exclusionary predictive marker [56].

Another recently published study showed that the number of somatic mutations and candidate neoantigens generated from these mutations may predict response to immune checkpoint inhibition in malignant melanoma [57].

A recent study showed that higher non-synonymous mutation burden in tumors was associated with improved objective response, durable clinical benefit, and progression-free survival in two independent cohorts [58]. Furthermore, smoking history, higher neoantigen burden, and DNA repair pathway mutations also correlated with efficacy of immune checkpoint inhibition [58]. However, these factors were also associated with mutation burden. Smoking status has been shown to correlate with response rate to anti-PD-L1 therapy in a variety of clinical trials [59, 60].

2.4.6 Microbiome

The gut microbiota plays an important role in shaping systemic immune resonses [61-63]. In the cancer context, a role for intestinal microbiota in mediating immune activation in response to chemotherapeutic agents has been demonstrated [64, 65]. Sivan et al. were among the first to show the impact of intestinal microbiota on response to immune checkpoint inhibitors [66]. They compared melanoma growth in mice harboring distinct commensal microbiota and observed differences in spontaneous antitumor immunity, which were eliminated upon cohousing or after fecal transfer. Sequencing of the 16S ribosomal RNA identified Bifidobacterium as associated with the antitumor effects. In their study, oral administration of Bifidobacterium alone improved tumor control to the same degree as PD-L1-specific antibody therapy, and combination treatment nearly abolished tumor outgrowth. Moreover, a study by Vétizou et al. confirmed the hypothesis that manipulating the microbiota might modulate cancer immunotherapy [67]. In their study they were able to show that antitumor effects of CTLA-4 blockade depend on distinct Bacteroides species. In mice and patients, T cell responses specific for Bacteroides thetaiotaomicron or Bacteroides fragilis were associated with the efficacy of CTLA-4 blockade.

2.5 Rationale for performing the trial

Despite multimodal therapy, the cure rate of patients with stage IIIA NSCLC is poor and therapy outcome failed to improve during the past years. The addition of immunotherapy with MEDI4736 as a novel treatment modality has the potential to improve the outcome without adding substantial toxicity to an otherwise intensive multimodality treatment, as MEDI4736 has been generally well tolerated. Based on the above mentioned evidence on immune checkpoint inhibition, there is a strong rationale to test this novel treatment modality also in the curative setting in order to improve local tumor control and prevent distant metastasis to improve the cure rate in this patient population.

A few other trials explore the role of immune checkpoint control in a curative setting. The PEARLS trial is a randomized phase III trial investigating adjuvant pembrolizumab in completely resected NSCLC patients with stage I-IIIA disease. The PACIFIC trial (NCT02125461) is a randomized phase III trial comparing consolidation therapy with MEDI4736 to placebo after definitive combined radio-chemotherapy. In contrast to these ongoing trials evaluating immunotherapy protocols in adjuvant settings, our trial will explore the addition of immune checkpoint inhibition already in the neoadjuvant setting.

To the best of our knowledge, our current trial is among one of the first trials worldwide investigating the therapeutic efficacy of PD1/PD-L1 inhibition before tumor resection and thus is at the forefront of the development of innovative approaches for the treatment of locally advanced NSCLC.

Rationale for neoadjuvant immune checkpoint inhibition

As immune checkpoint inhibition with the anti-PD-L1 antibody MEDI4736 induces an antitumor immune response in metastatic patients, the use of this approach prior surgical resection of the tumor is justified. The tumor is probably inducing and maintaining the host immune response by its immunogenicity. Furthermore, it is expected that neoadjuvant chemotherapy will increase tumor immunogenicity through increased antigen release due to tumor cell destruction.

We opted to administer two cycles of neoadjuvant MEDI4736. On one hand, this allows for surgical resection, which is an established standard procedure after induction chemotherapy, at an early

time point. On the other hand, it is known from trials in palliative setting that more than half of the patients showing an objective response to immune checkpoint inhibition have already a reduction in tumor size at the first radiographic re-evaluation. Moreover, neoadjuvant administration of MEDI4736 gives a unique opportunity to evaluate the mechanisms of immune response and induction of antitumor immunity in the resected tumor tissue. Hence, the trial also includes a vast array of translational research questions.

The addition of 2 cycles of neoadjuvant immunotherapy after neoadjuvant chemotherapy delays surgical resection. However, it is well known that patients showing progressive disease very shortly after the end of chemotherapy have a dismal prognosis that cannot be improved by surgery.

Rationale for adjuvant immune checkpoint inhibition

It is hypothesized from preclinical data that immunotherapy may work best in the situation of minimal residual disease. The adjuvant setting is therefore the ideal clinical scenario to test the exact place of immunotherapy with immune checkpoint inhibitors to improve the cure rate of lung cancer patients after surgery. A role for immune checkpoint inhibition in adjuvant setting was recently demonstrated for melanoma. In the EORTC 18071 trial, adjuvant therapy with the CTLA-4 antibody ipilimumab significantly improved recurrence-free survival in stage III malignant melanoma [68]. The randomized US intergroup phase III trial (E1609) is currently investigating standard high-dose interferon alfa-2b vs. ipilimumab in stage III-IV melanoma after surgical resection. In the palliative setting these agents are usually given for up to one or two years and have demonstrated long lasting disease control. We therefore decided for treatment duration of one year after tumor resection.

Rationale for fixed dose of MEDI4736

A population PK model was developed for MEDI4736 using monotherapy data from a Phase I study (*study 1108; N=292; doses= 0.1 to 10 mg/kg q2w or 15 mg/kg q3w; solid tumors*). Population PK analysis indicated only minor impact of body weight on PK of MEDI4736 (coefficient of ≤ 0.5). The impact of body weight-based (10 mg/kg q2w) and fixed dosing (750 mg q2w) of MEDI4736 was evaluated by comparing predicted steady state PK concentrations (5^{th}, median and 95^{th} percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body weight of ~75 kg). A total of 1000 patients were simulated using body weight distribution of 40–120 kg. Simulation results demonstrate that body weight-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-subject variability with fixed dosing regimen.

Similarly, a population PK model was developed for tremelimumab using data from Phase I through Phase III (*N=654; doses= 0.01 to 15 mg/kg q4w or q90d; metastatic melanoma*) [69]. Population PK model indicated minor impact of body weight on PK of tremelimumab (coefficient of ≤ 0.5). The weight-based (1 mg/kg Q4W) and fixed dosing (75 mg/kg q4w; based on median body weight of ~75 kg) regimens were compared using predicted PK concentrations (5^{th}, median and 95^{th} percentiles) using population PK model in a simulated population of 1000 patients with body weight distribution of 40 to 120 kg. Similar to MEDI4736, simulations indicated that both body weight-based and fixed dosing regimens of tremelimumab yield similar median steady state PK concentrations with slightly less between-subject variability with fixed dosing regimen.

Similar findings have been reported by others [70-73]. Wang and colleagues investigated 12 monoclonal antibodies and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies [71]. In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-subject variability in pharmacokinetic/pharmacodynamics parameters [72].

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar pharmacokinetic exposure and variability, we considered it feasible to use fixed dosing regimens. Based on average body weight of 75 kg, a fixed dose of 750 mg q2w MEDI4736 (equivalent to 10 mg/kg q2w) is included in the current study.

2.6 Choice of design

Rationale for single arm phase II design

Immune checkpoint inhibition with anti-PD-L1 antibodies is a novel treatment approach. So far, the only published data were generated from phase I and single-arm phase II trials in other indications than lung cancer. Our trial is to our knowledge the first study investigating the neoadjuvant use of an immune checkpoint inhibitor in locally advanced NSCLC. As the Lung Cancer Project Group of the SAKK has a long standing interest in stage IIIA(N2) disease, robust historical data from previous trial exist and will serve as comparator for the current trial. Furthermore, the trial selects the same patient population (same inclusion and exclusion criteria) and the same chemotherapy backbone. That will give us the opportunity to put the results of the present trial into clinical perspective.

2.7 Choice of trial population

We will include patients with stage IIIA(N2) disease as most of these patients are amenable for curative resection and still in need of more efficacious therapeutic options.

Patients will not be selected based on histological subtype or genomic aberrations as these parameters do currently not influence treatment choice in the advanced disease setting.

Patients will also not be pre-screened for PD-L1 expression since the predictive role of PD-L1 expression in the tumor tissue is still unclear and should not guide treatment decisions for immune checkpoint inhibition. Furthermore, the use of PD-L1 expression status by immunohistochemistry as a predictive biomarker is currently still cofounded by multiple unresolved issues: variable detection antibodies, differing cut-off values in immunohistochemistry, tissue preparation, processing variability, primary versus metastatic biopsies, oncogenic versus induced PD-L1 expression, and staining of tumor versus tumor-infiltrating immune cells.

3 OBJECTIVES AND ENDPOINTS

3.1 Objective

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

3.2 Endpoints

For definition of endpoints see section 13.

3.2.1 Primary endpoint

The primary endpoint of the trial is:

- Event-free survival (EFS) at 12 months

3.2.2 Secondary endpoints

Secondary endpoints of the trial are:

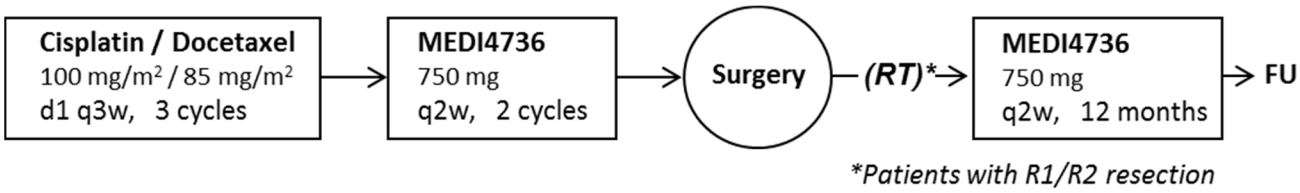
- EFS
- Overall survival (OS)
- Objective response (OR) after neoadjuvant chemotherapy
- OR after neoadjuvant immunotherapy
- Pathological complete response (pCR)
- Major pathological response (10% or less residual viable tumor)
- Rate of nodal down-staging to < ypN2
- Complete resection
- Pattern of recurrence (local, loco-regional, distant)
- Adverse events (AEs)
- Postoperative 30-day mortality

3.3 Additional research questions

- Comparison of the tumor immunome before (treatment-naïve) and 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 endpoints of interest (EFS, OS and OR after neoadjuvant immunotherapy) in NSCLC. Historical control samples from previous SAKK trials will be used.
- Investigation of the effect of the gut microbiota on the response to immunotherapy (***optional***).

4 TRIAL DESIGN

Multicenter, single-arm, phase II trial



Please refer to sections 9 and 10 of this protocol for details on the treatment schedule and for instructions on treatment delays or premature discontinuation.

5 TRIAL DURATION AND TERMINATION

The inclusion of patients is planned to start in Q1 2016 and will stop after the inclusion of 68 patients, which is expected in Q1 2019. End of trial treatment is expected for Q3 2020.

All patients will have a lifelong follow-up. The trial team reserves the right to evaluate if the follow-up period can be stopped earlier.

The trial may be stopped prematurely based on the results of an interim safety analysis (see section 15). In addition, accrual may be interrupted and/or the trial may be stopped early if new scientific data become available which substantially change the benefit/risk ratio. Decision on premature termination will be made by the SAKK Board.

6 SELECTION OF PATIENTS

For timelines see section 12.

6.1 Inclusion criteria

To be eligible to enter this trial, patients must fulfill the following criteria.

6.1.1 Written informed consent according to ICH-GCP regulations before patient registration and any protocol-related procedures.

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

6.1.3 Tumor tissue is available for the mandatory translational research (preferably histology, cytology allowed).

6.1.4 Tumor stage T1-3N2M0 (stage IIIA(N2) according to the TNM classification, 7th edition, October 2009 (see Appendix 2). Mediastinal lymph node staging has to follow the process chart depicted in Appendix 6.

6.1.5 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 [74].

6.1.6 Measurable disease according to RECIST 1.1 criteria (non-nodal lesions ≥10 mm in longest diameter, lymph nodes ≥15 mm in short axis) by PET/CT with contrast enhanced CT-scan.

6.1.7 WHO performance status 0-1 (see Appendix 4).

6.1.8 Age 18-75 years at time of registration.

6.1.9 Appropriate lung function based on the ESTS guidelines (see Appendix 7) [75]:

- 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%.

6.1.10 Adequate hematological values: hemoglobin ≥ 90 g/L, absolute neutrophils count ≥ 1.5 x 10^9/L, platelets count ≥ 100 x 10^9/L.

6.1.11 Adequate hepatic function: bilirubin ≤ 1.5 x ULN, AST/ALT ≤ 1.5 x ULN, AP ≤ 2.5 x ULN.

6.1.12 Adequate renal function: calculated creatinine clearance ≥ 60 mL/min, according to the formula of Cockcroft-Gault (see Appendix 3).

6.1.13 Women with child-bearing potential are using effective contraception (double method, see 9.8) are not pregnant or lactating and agree not to become pregnant during participation in the trial and during 90 days after the last treatment. A negative serum pregnancy test performed within 7 days before registration into the trial is required for all women with child-bearing potential. Men agree not to father a child during participation in the trial and during 90 days after the last treatment.

6.1.14 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.

6.2 Exclusion criteria

Any potential patient who meets any of the following criteria has to be excluded from entering the trial.

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

6.2.2 Sulcus superior tumors (Pancoast tumors).

6.2.3 Previous or concomitant malignancy within 5 years prior registration with the exception of adequately treated localized non-melanoma skin cancer or cervical carcinoma in situ.

6.2.4 Any previous treatment for NSCLC.

6.2.5 Any previous treatment with a PD-1 or PD-L1 inhibitor, including MEDI4736.

6.2.6 Previous radiotherapy to the chest.

6.2.7 Absolute contraindications for the use of corticosteroids as premedication.

6.2.8 Concurrent treatment with other experimental drugs or other anticancer therapy, treatment in a clinical trial within 30 days prior to registration.

6.2.9 Current or prior use of immunosuppressive medication within 28 days before the first dose of MEDI4736, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses (i.e. which must not exceed 10 mg/day of prednisone or an equivalent corticosteroid) and the premedication for chemotherapy.

6.2.10 Severe or uncontrolled cardiac disease requiring treatment, congestive heart failure NYHA III or IV (see Appendix 5), unstable angina pectoris even if medically controlled, history of myocardial infarction during the last 3 months, serious arrhythmias requiring medication (with exception of atrial fibrillation or paroxysmal supraventricular tachycardia).

6.2.11 Mean QT interval corrected for heart rate (QTc) ≥470 ms calculated from 3 ECGs using Bazett's Correction.

6.2.12 Preexisting peripheral neuropathy (> Grade 1).

6.2.13 Body weight less than 30 kg.

6.2.14 Active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease or a syndrome that requires systemic steroids or immunosuppressive agents.

Exceptions: Vitiligo or resolved childhood asthma/atopy

Hypothyroidism stable on hormone replacement or Sjorgen's syndrome

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

6.2.16 Known evidence of acute or chronic hepatitis B, hepatitis C or human immunodeficiency virus (HIV) infection.

6.2.17 History of primary immunodeficiency.

6.2.18 History of allogeneic organ transplant.

6.2.19 Known history of previous clinical diagnosis of tuberculosis.

6.2.20 Receipt of live attenuated vaccination any time during trial therapy with MEDI4736 and within 30 days of receiving the last dose of MEDI4736.

6.2.21 Any concomitant drugs contraindicated for use with MEDI4736: this includes systemic corticosteroids (exceptions see 6.2.9), methotrexate, azathioprine, and tumor necrosis factor (TNF)-α blockers. Any concomitant drugs contraindicated for use with the other trial drugs according to the locally approved product information.

6.2.22 Known hypersensitivity to trial drugs (cisplatin and docetaxel), to the IMP or to any excipient.

6.2.23 Any other serious underlying medical (e.g. uncontrolled diabetes mellitus, active uncontrolled infection, active gastric ulcer, uncontrolled seizures, severe hearing impairment), psychiatric, psychological, familial or geographical condition that, 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.

7 REGISTRATION

7.1 Pre-registration procedure

Prior to registration, the following steps have to be performed:

- Fill in the patient screening and enrollment list,
- Check the eligibility criteria,
- Check the availability of tumor tissue (preferably histology, cytology allowed) for the retrospective central pathology review (refer to section 17 for further information),
- Check resectability based on a multidisciplinary tumor board decision,
- Obtain written informed consent from the patient prior to any protocol-specific procedure
  - Main PIS/IC, mandatory for trial participation

    (*consent for the mandatory translational research and for the optional research question with stool is incorporated in the main PIS/IC*)
  - PIS/IC biobank, optional for trial participation,
- Baseline blood for the mandatory translational research can be collected from 14 days prior to registration until the first day of trial treatment (*prior* to the administration of the first treatment dose), at the latest; samples have to be shipped immediately upon collection (refer to section 18 for details).
- Baseline stool for the *optional* translational research can be collected from 14 days prior to registration until the first day of trial treatment (prior to the administration of the first treatment dose), at the latest.
  If applicable, instruct the patient and dispense the stool collection kit (refer to section 18 for details).

7.2 Registration procedure

Registration is done via Internet (www.sakk.ch/edc).

Only if this is not possible due to technical problems, e.g. unavailability of the web-based electronic data capture (EDC) system: by faxing the completed, dated and signed paper version of the eligibility ("form E") case report form (CRF) to the SAKK CC.

Fax +41 31 508 41 42

(Opening hours: Monday to Friday 8:00 a.m. to 5:00 p.m.)

In order to receive authorization for online registration and data entry, sites must send a copy of the completed staff list (available on the SAKK website) to the SAKK CC. Login details for the EDC system will be sent to authorized persons within 2 working days.

The SAKK CC will be closed on the following days:

1st January	1st August (National holiday)*
2nd January	4th Monday of November, from 3:00 pm
Good Friday (Friday before Easter)*	24th December (from 12:00 noon)
Easter Monday	25th December
Ascension Thursday*	26th December
Whit Monday (Pentecost)	31st December (from 12:00 noon)

* The SAKK CC will close at 4:00 pm on weekdays before these holidays.

7.3 After registration

- Report the medical history, baseline clinical and laboratory information, tumor location and baseline symptoms in the electronic (e)CRFs,
- Update the screening and enrollment list,
- Fill in the patient identification list,
- Tumor samples must be sent to Central Pathology for review at the latest 30 days after registration (refer to section 17 for further details).
- Ensure that blood (and stool from consenting patients) has been or will be shipped to the research laboratory (refer to section 18).

The printout of the eCRF form ("form ER"), dated and signed by the treating investigator (authorized physician according to the staff list), has to be sent to the SAKK CC by email or fax within one month after registration.

Trial therapy should be started within 7 days from registration.

8 DRUG SUPPLY AND HANDLING

8.1 Drugs in protocol

8.1.1 Investigational medicinal product (IMP)

For this trial MEDI4736 (durvalumab) is the IMP.

MEDI4736 is a human mAb of the IgG1 kappa subclass directed against PD-L1. It contains a triple mutation in the constant domain of the IgG1 heavy chain that reduces binding to C1q and Fcγ receptor.

MEDI4736 is an investigational product which is not approved for any indication in any country.

8.1.2 Other drugs for anticancer treatment

Cisplatin and docetaxel are approved in Switzerland, in Europe and in the USA for the treatment of NSCLC and are not investigational drugs in the context of this trial. Cisplatin and docetaxel will be given pre-operatively and prior to MEDI4736 as standard backbone treatment according to their Swissmedic-approved indication, the applicable safety precautions and the Swiss law.

For both drugs, generic products do exist and may be used.

8.2 Drug supply and handling of MEDI4736

8.2.1 Drug supply

MEDI4736 will be supplied by the Investigational Products Supply section of AstraZeneca/MedImmune as a concentrate solution for infusion and provided free of charge by SAKK to all study sites. The distribution will be managed by an authorized pre-wholesaler located in Switzerland.

Instructions on ordering and shipment, and a drug order form are provided in separate documents which can be downloaded from the SAKK website (www.sakk.ch → Members → Trials → Lung Cancer → SAKK 16/14 → Useful tools → IMP).

8.2.2 Handling and safety of MEDI4736

Refer to the current version of the IB for the handling and safety of the IMP [47].

MEDI4736 is formulated at a concentration of 50 mg/mL in 26 mM histidine/histidine-HCl, 275 mM trehalose dihydrate, 0.02% [weight/volume] polysorbate 80, pH 6.0. The investigational product is supplied as a vialed liquid solution in clear 10R glass vials closed with an elastomeric stopper and a flip-off cap overseal.

Each vial contains 500 mg (nominal) of active investigational product at a concentration of 50 mg/mL (500 mg/vial).

Unopened vials of liquid MEDI4736 must be stored at 2°C to 8°C. MEDI4736 must be used within the individually assigned expiry date noted on the label. Vials must be used for specific subjects and must not be shared between patients.

The handling of open vials and the in-use storage and stability are described in section 9.3.2.

8.2.3 Labeling of MEDI4736

The IMP will be labeled in English. The following information will be indicated on the label:

SAKK 16/14
MEDI4736 500 mg in 10 mL (50 mg/mL); for infusion; Store at 2°C to 8°C
For use in clinical trial only / Free of charge
Batch Number
Expiry date
Name of site: _____
Name of principal investigator: _____
UPN: 16/14_ _____

Dispensing date: _____
SAKK - Swiss Group for Clinical Cancer Research, Effingerstrasse 33, CH - 3008 Bern,
Phone: +41 31 3899191

8.2.4 Dispensing and accountability of MEDI4736

The unique patient number (UPN), as well as the names of the site and principal investigator, must be written on the label of the bottle as soon as MEDI4736 is dispensed.

Trained personnel should prepare infusion bags under aseptic conditions. The solution will be diluted with 0.9% [weight/volume] saline for i.v. infusion, according to the instructions provided in section 9.3.2.

Please ensure the use of the drug inventory log (available on www.sakk.ch → Members → Trials → Lung Cancer → SAKK 16/14 → Useful tools → IMP), which must be kept up-to-date and identify the receipt and dispensing of the drug (including date, amount, batch number, UPN).

8.2.5 Unused MEDI4736

Unused, partly unused or expired trial medication will be destroyed at the site according to local guidelines.

The destruction of unused or expired medication should take place at the conclusion of the trial, upon approval by the Clinical Research Associate (CRA) and is to be documented on the drug inventory log and additionally, in the trial-specific IMP destruction certificate (provided by SAKK and available on the SAKK website).

8.3 Drug supply and handling of cisplatin and docetaxel

8.3.1 Drug supply

Cisplatin and docetaxel are applied within their approved indication and will thus be prescribed and purchased according to the routine procedures of the participating sites.

8.3.2 Handling and safety of cisplatin and docetaxel

Both drugs will be administered as a background medication, according to the approved dose and schedule for NSCLC, following the locally established clinical routine and national as well as international treatment guidelines [18, 35, 76].

For handling and safety of cisplatin and docetaxel, please refer to the respective product information (which can be downloaded from www.swissmedicinfo.ch). National guidelines on handling of cytostatic drugs have to be considered (e.g. in Switzerland: [77]).

8.4 Product quality complaint handling

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, packaging, shipment and storage (e.g. wrong storage condition during transport). A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from clinical trials are crucial for the protection of patients, investigators and the sponsor, and are mandated by regulatory agencies worldwide.

8.4.1 Procedures

In case site staff identifies a potential product complaint situation, the product is placed in quarantine and SAKK CC must be contacted immediately.

PQCs must be forwarded within 24 hours to the SAKK CC (form available on www.sakk.ch → Members → Trials → Lung Cancer → SAKK 16/14). If the defect is combined with a SAE/SAR, the site staff must additionally report the event to SAKK CC according to the reporting timelines for SAEs (see section 11). SAKK CC will inform the site how to proceed with the suspected product.

9 TRIAL TREATMENT

9.1 Treatment overview

- Neoadjuvant chemotherapy with cisplatin and docetaxel: 3 cycles of 21 days
  - Cisplatin 100 mg/m^2 d1 (corresponds to day 1, 22, 43 / week 1, 4, 7)
  - Docetaxel 85 mg/m^2 d1 (corresponds to day 1, 22, 43 / week 1, 4, 7)
- Neoadjuvant immunotherapy with MEDI4736: 2 cycles of 14 days
  - MEDI4736 750 mg d1 (corresponds to day 64, 78 / week 10, 12)
- Surgery
  - Between 2 and 4 weeks after the last application of MEDI4736
    (corresponds to days 92-106 / week 14-16)
- Radiotherapy
  recommended for R1/R2 resection (incl. extracapsular spread of mediastinal LN metastases)
  - Between 2 and 4 weeks after surgery
- Adjuvant immunotherapy with MEDI4736
  Should start within 4-6 weeks after surgery or within 2 weeks after completion of radiotherapy
  - MEDI4736 750 mg d1 every 2 weeks for a max. of 1 year (26 cycles)

Week	**1**	**4**	**7**	**10**	**12**	**14-16** a)	**18-22** b) c)	**20-24**	**…**	**70-74** d)
Day	1	22	43	64	78	92-106	120-148	134-162		
Cisplatin 100 mg/m^2	**x**	**x**	**x**			**Surgery**				
Docetaxel 85 mg/m^2	**x**	**x**	**x**							
MEDI4736 750 mg				**x**	**x**		**x**	**x**	**…**	**x**

a) Surgery must be performed between 2 and 4 weeks after the last application of immunotherapy.

b) Adjuvant MEDI4736 treatment should start between 4-6 weeks after surgery (for R0 patients or when no RT is applied).

c) For patients with R1/R2 resection, incl. extracapsular spread of mediastinal lymph node metastases, who will receive post-surgery radiation therapy: radiotherapy should start 4-6 weeks after surgery; the first infusion of adjuvant MEDI4736 should take place within 2 weeks after completion of radiotherapy.

d) Adjuvant immunotherapy is administered for a maximum of 1 year (26 cycles).

9.2 Chemotherapy with cisplatin/docetaxel

Please refer to the respective locally approved product information sheets for detailed information on handling and safety of cisplatin and docetaxel (also available online at www.swissmedicinfo.ch).

9.2.1 Schedule

Neoadjuvant chemotherapy with cisplatin and docetaxel is administered as backbone treatment and according to the current standard of care in Switzerland (based on trials SAKK 16/96 and SAKK 16/00). The treatment is given for a total of 3 cycles (21 days each).

The second and third cycles start on day 22 and day 43 respectively, provided neutrophils are ≥ 1.0 x 10^9/L and thrombocytes are ≥ 100 x 10^9/L. Otherwise, treatment is temporarily interrupted until recovery for a maximum of two weeks.

If treatment cannot be resumed after a maximum delay of two weeks, chemotherapy will be discontinued permanently and the patient may proceed to anti-PD-L1 therapy (the possibility to go to the next treatment step should be evaluated with the coordinating investigators).

9.2.2 Dose and administration

Docetaxel should be given before cisplatin, as follows:

- docetaxel 85 mg/m^2 1 hour i.v. infusion d1 then
- cisplatin 100 mg/m^2 1 hour i.v. infusion d1

A split dose of cisplatin (50 mg/m^2 day 1 and day 2) is allowed at the discretion of the local investigator.

The use of cisplatin is mandatory in the 1st cycle. However, cisplatin can be replaced by carboplatin for the 2nd and 3rd cycle of neoadjuvant chemotherapy in case of cisplatin-induced toxicity. Carboplatin should be dosed as follows: carboplatin AUC6 (Calvert formula: carboplatin in mg = AUC x (CrCl + 25)).

The use of generic drugs for cisplatin and docetaxel is allowed.

Refer to section 10.7 for details on the measures to be taken in the occurrence of AEs during chemotherapy.

9.2.3 Premedication

Premedication with dexamethasone is mandatory. Recommendation: 8 mg x 2 p.o. one day before chemotherapy (d-1) and for an additional 2 days (i.e. d1 & d2) at each chemotherapy cycle. Application scheme as per local practice is also accepted.

9.2.4 Supportive medication

Hydration and anti-emetic therapy are to be performed according to the ESMO/MASCC guidelines for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting [78] and at the discretion of the treating investigator.

Granulocyte-Colony Stimulating Factor (G-CSF)

G-CSF must be administered during all three chemotherapy cycles.

Recommended doses: G-CSF 30 millions of units for patients up to 75 kg and 48 millions of units above 75 kg on day 3 to 8 (5 days minimum) or pegfilgrastim as a single dose of 6 mg on day 5 of each cycle.

9.2.5 Warnings and precautions

Surveillance during treatment with docetaxel

In case a docetaxel hypersensitivity reaction occurs despite premedication, it is very likely to occur within a few minutes from the start of the first or of the second infusion of docetaxel. Therefore, during the 1st and the 2nd infusion, a careful evaluation of general sense of well-being should be performed. Whenever possible monitoring of blood pressure and heart rate has to be performed by a physician or nurse for at least the first 10 minutes, so that immediate intervention could occur in response to symptoms of an untoward reaction.

Facilities and equipment for resuscitation should be immediately available: antihistamine, corticosteroids, aminophylline and epinephrine.

9.3 Immunotherapy with MEDI4736

Detailed information on handling and safety of the IMP is provided in the IB [47] and in the toxicity management guidelines (see protocol section 10.8).

Investigators should be familiar with the current version of the IB.

9.3.1 Schedule

In neoadjuvant setting:

MEDI4736 will be administered on day 1 of each cycle, for 2 cycles of 14 days each, after treatment with cisplatin/docetaxel.

MEDI4736 therapy should start on day 1 of week 10 after completion of chemotherapy. In case of interruptions or premature discontinuation of chemotherapy, MEDI4736 treatment should start 3 weeks after the last dose of chemotherapy (provided AEs are resolved as described in section 10.7) but no later than 5 weeks after the last dose of chemotherapy.

Of note: all patients have to undergo a radiological re-assessment within one week before starting MEDI4736 (see section 12.2).

In adjuvant setting:

MEDI4736 will be administered every 14 days for 1 year (on day 1 of each cycle, maximum 26 cycles).

- For patients with R0 resection or when no radiotherapy is applied, the first infusion should start within 4-6 weeks after surgery (e.g. week 18-22 from the start of chemotherapy when no treatment delays occurred).
- For patients with R1/R2 resection who will undergo post-surgery radiotherapy, the first infusion of adjuvant MEDI4736 should take place within 2 weeks after completion of radiotherapy.

9.3.2 Dose and administration

A fixed dose of 750 mg MEDI4736 will be administered at room temperature (approximately 25°C) by controlled infusion via an infusion pump into a peripheral or central vein.

The preparation of infusion bags should be done under aseptic conditions by trained personnel.

The calculated volume of MEDI4736 is added to the i.v. bag, and the bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag. The final concentration of MEDI4736 must be between 1-20 mg/ml.

In-use storage and stability

Total in-use storage time from needle puncture of MEDI4736 vial to start of administration should not exceed 4 hours at room temperature or 24 hours at 2-8°C. If in-use storage time exceeds these limits, a new dose must be prepared from new vials. Infusion solutions must be allowed to equilibrate to room temperature prior to commencement of administration. MEDI4736 does not contain preservatives and any unused portion must be discarded.

Prior to the start of the infusion, ensure that the bag contents are at room temperature to avoid an infusion reaction due to the administration of the solution at low temperatures. Vials must be used for specific subjects and must not be shared between patients.

Following preparation of MEDI4736, the entire contents of the i.v. bag should be administered as an i.v. infusion over approximately 60 minutes (±5 minutes), using a 0.2-µm in-line filter.

The i.v. line will be flushed with a volume of normal saline equal to the priming volume of the infusion set used after the contents of the i.v. bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered.

Of note*:* Alternatively to saline 0.9%, MEDI4736 could also be diluted in 5% (w/v) dextrose. Since the compatibility of MEDI4736 with other i.v. medications and solutions, other than normal saline 0.9% and dextrose 5% is not known, the MEDI4736 solution should not be infused through an i.v. line in which other solutions or medications are being administered.

9.3.3 Premedication

In the event of an infusion-related reaction, premedication may be used before the next infusion (see section 10.8.2 for management guidelines). Prescription of acetaminophen or diphenhydramine is allowed.

9.3.4 Supportive medication

None.

9.3.5 Warnings and precautions

As with the administration of any immunoglobulin (Ig), infusion reactions and acute IgE-mediated allergic reactions may occur, may be severe and may result in death. Patients must be monitored during and after infusion with assessment of vital signs at the times specified in section 12.

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.

Although MEDI4736 is a human mAb, it is possible for humans to develop antidrug antibodies. The occurrence of such antidrug antibodies could result in immune complex disease (with manifestations such as arthralgia, serum-sickness, abdominal pain, back pain, and vasculitis) or altered MEDI4736 levels or activity.

Owing to the drug's mechanism of action and nonclinical findings, patients should be monitored for the development of immune-mediated reactions such as enterocolitis, dermatitis, hepatitis/hepatotoxicity, endocrinopathy, pneumonitis, neuropathy, serious infection, infusion-related reactions, anaphylaxis or serious allergic reaction and immune complex disease.

Refer to section 10.8 for toxicity management guidelines during MEDI4736 treatment.

9.4 Surgery

Surgery is to be performed within 2-4 weeks after the last application of MEDI4736.

Tumor resection includes an anatomical resection with a mediastinal lymph node dissection as previously described by Lardinois et al. [79]. Anatomical resection can be pneumonectomy, lobectomy, bilobectomy or sleeve procedures. Tumor resection can be performed using an open approach or the video-assisted thoracoscopy (VATS) technique. Due to the fact that no prospective randomized studies have demonstrated an oncological equivalence of limited resection compared to lobectomy in early stage NSCLC, limited resection procedures (e.g. segmentectomy) are not allowed in this trial and patients functionally not eligible for at least a lobectomy have to be excluded.

In the case of T3 tumors with infiltration of the chest wall, an en bloc resection of the lobe with a part of the chest wall with a sufficient resection margin will be performed. In the case of infiltration of the mediastinum (T3 with infiltration of the phrenic nerve, of the mediastinal pleura, of the peridardium, or of the diaphragm), an en bloc resection should be possible.

N2 disease is considered as unresectable when mediastinal nodes are bulky fixed with no visible tissue plane between nodes and trachea or invasion of the great vessels (aorta, pulmonary trunk or superior vena cava) or heart on radiological exams. In case of doubt, mediastinoscopy should be performed to rule out tracheal or carinal invasion.

The treating investigator should contact the supporting surgeons in case of uncertainties or questions.

9.5 Postoperative radiotherapy

Postoperative radiotherapy is highly recommended for patients with R1/R2 resection, including patients with extracapsular spread of mediastinal lymph node metastases.

For all other patients the use of postoperative radiotherapy is not permitted.

Radiotherapy should start 4-6 weeks after surgery and is to be performed in accordance with the standard of care for this patient group and will follow the institutional guidelines.

The treating investigator should contact the coordinating investigators in case of questions.

9.6 General remarks on dose modifications and delays

Cisplatin and docetaxel must not be delayed for longer than 2 weeks (also for vacations). Doses omitted for AEs are not replaced. Once the dose of the chemotherapeutic drug has been reduced for any type of AE, it must not be increased at a later date.

If a patient has to permanently discontinue chemotherapy early due to high-grade or persistent AE (> 2 weeks) and there is no evidence of progressive disease, he/she will proceed to MEDI4736 therapy if possible.

Neoadjuvant MEDI4736 must not be delayed for longer than 2 weeks (also for vacations).

If a patient has to permanently discontinue MEDI4736 treatment in the neoadjuvant setting due to high-grade or persistent AE (> 2 weeks) and there is no evidence of progressive disease, he/she may proceed to surgery if possible.

Adjuvant MEDI4736 must not be delayed for longer than 6 weeks in case of AEs (also for vacations).

If a patient has to permanently discontinue MEDI4736 treatment in the adjuvant setting due to high-grade AEs or AEs persisting for longer than 4 weeks, he/she will enter the follow-up phase.

AE-specific dose modifications are described in sections 10.7 and 10.8. For all AEs that are not mentioned in these sections, refer to the corresponding locally approved product information for cisplatin and docetaxel or the IB for MEDI4736, respectively. In case of conflicting recommendations, use the most restrictive treatment adjustment.

The coordinating investigators should be contacted in case the investigator has any doubts about treatment delays and/or dose modifications.

9.7 Treatment duration

Patients will be transferred to the follow-up phase as soon as one of the following events occurs:

- Treatment was completed as per protocol,
- Occurrence of an event (i.e. relapse/progression or second tumor; see section 13.2.1),
- Unacceptable toxicity,
  The possibility to go to the next treatment step should be evaluated with the coordinating investigators (refer to section 9.6 above),
- Patient refusal (see section 20.4 on premature withdrawal),
- Withdrawal by the physician (see section 20.4 on premature withdrawal),
- Resection according to protocol cannot be performed,
- Treatment with cisplatin/docetaxel or neoadjuvant MEDI4736 has to be delayed for more than 2 weeks (also for vacations),
  The possibility to go to the next treatment step should be evaluated with the coordinating investigators (refer to section 9.6 above),
- Treatment with adjuvant MEDI4736 has to be delayed for more than 6 weeks (also for vacations),
- Initiation of alternative anticancer treatment including another investigational agent (see section 9.8 below),
- Patient becomes pregnant.

If incorrectly enrolled, patients should discontinue treatment. The patient may resume treatment after an evaluation of any potential safety concerns with the coordinating investigators.

All patients will be followed up lifelong (unless the SAKK Board decides on premature trial termination).

See section 12.8 for evaluations after treatment termination.

No trial-specific assessments will be performed after recurrence.

9.8 Treatments not permitted during trial treatment phase

The following treatments are not permitted during the trial treatment phase:

- Other anticancer treatments,
- Investigational treatments,
- Immunosuppressive medications (such as but not limited to: methotrexate, azathioprine, and TNF-α blockers) within 28 days of the first dose of MEDI4736
  Exception:
  - systemic corticosteroids at doses not exceeding 10 mg/day of prednisone or equivalent
  - premedication for neoadjuvant chemotherapy
  - immunosuppressive medications for the management of MEDI4736-related AEs or in patients with contrast allergies
  - inhaled and intranasal corticosteroids,
- Live attenuated vaccination within 30 days of MEDI4736 dosing (i.e. 30 days prior to the first dose, during treatment with MEDI4736 and for 30 days after discontinuation of MEDI4736). Inactivated viruses, such as those in the influenza vaccine, are permitted.

9.9 Precaution

9.9.1 Contraception

The following precaution is valid for women taking part in the clinical trial:

Women of childbearing potential who are sexually active with a non-sterilized male partner must use two methods of effective contraception from inclusion, and must agree to continue using such precautions for at least 90 days after the final dose of trial drugs or following the last infusion of MEDI4736. Cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method or the withdrawal method are not acceptable methods of birth control.

- Women of childbearing potential are defined as those who are not surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or postmenopausal (defined as 12 months with no menses without an alternative medical cause).
- Women must use two acceptable methods of effective contraception as described in the table below. Effective contraceptives can be hormonal (e.g. contraceptive pill, injections, or implants) or mechanical (e.g. condom, intrauterine pessar, diaphragm, cervical cap or another device). Women using mechanical contraceptives have to combine two methods of mechanical contraception (like condom, coil, diaphragm or another device). Women using hormonal contraceptives must use one additional method of mechanical contraception.

The following precaution is valid for men taking part in the clinical trial:

- Non-sterilized males who are sexually active with a female partner of childbearing potential must use two acceptable methods of effective contraception (see table below) from registration and for 90 days after receipt of the final dose of trial drugs or MEDI4736.
- Males should refrain from fathering a child or donating sperm during the study and for 90 days following the last dose of MEDI4736.

Effective methods of contraception (two methods must be used) are:

Barrier Methods	**Intrauterine Device Methods**	**Hormonal Methods**
Male condom plus spermicide	Copper T	Implants
Cap plus spermicide	Progesterone T[1]	Hormone shot or injection
Diaphragm plus spermicide	Levonorgestrel-releasing intrauterine system (e.g. Mirena®)[1]	Combined pill / Minipill Patch

[1]This is also considered a hormonal method

9.9.2 Blood donation

Patients should not donate blood during trial treatment and for at least 90 days following the last infusion of MEDI4736.

10 ADVERSE EVENT REPORTING, DOSE MODIFICATIONS AND SUPPORTIVE TREATMENT

The principal investigator is responsible for ensuring that all local staff involved in the trial is familiar with the content of this section.

10.1 Definition of AE

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure (as defined in ICH-GCP).

10.2 Reporting of AEs

Patients will be instructed by the investigator to report the occurrence of any AE.

The investigator assesses and records all AEs observed during the AE reporting period from registration until 30 days after administration of last dose. This 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. The investigator assesses the event for severity, relation to trial treatment and possible etiologies, and whether the event meets the criteria of an SAE (see section 11).
AEs ongoing beyond the end of the reporting period need to be followed up until resolution, stabilization (with the expectation that it will remain chronic) or start of alternative anticancer therapy.

AEs are coded with the NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.03, and assigned a Grade (from 1 = mild to 5 = death related to AE) as well as a relationship to trial treatment. The NCI CTCAE v4.03 (as pdf) as well as instructions on how to use the criteria can be found on http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Note:

- Report the start and end date of the event and any changes in grading observed within the reporting period.
- Baseline symptoms will be recorded on the CRF and will continue to be followed up during treatment.
- AEs are documented by the codes according to CTCAE v4.03. If none of the codes are applicable, it exists for each of the 26 system organ classes (SOCs) the term 'others' to describe the AE. If the term 'others' is applicable, briefly describe the AE in a comprehensive and understandable manner.
- Laboratory values will be documented as absolute values on the CRFs and should not be recorded as AE in addition. Out of range laboratory values occurring outside of predefined assessment times or any laboratory values not specifically asked to be assessed by the protocol should only be documented as AE if they are Grade 3 or higher.
- Weight and blood pressure measurements will be documented as absolute values on the CRFs and should not be recorded as AE in addition. Exception: AE hypertension to be documented if a therapy is indicated.
- Relationship of AEs to treatment is assessed using the following scale:

  1 Unrelated The adverse event is clearly not related to the trial treatment. The AE is completely independent of trial treatment and/or evidence exists that the event is definitely related to another etiology.

  2 Unlikely The adverse event is doubtfully related to the trial treatment. Temporal association between the AE and the trial treatment and the nature of the event is such that the trial treatment is not likely to have had any reasonable

association with the observed illness/event (cause and effect relationship improbable but not impossible).

3 Possibly The adverse event may be related to the trial treatment. Less clear temporal association; other etiologies also possible.

4 Probably The adverse event is likely related to the trial treatment. Clear-cut temporal association and a potential alternative etiology are not apparent.

5 Definitely The adverse event is clearly related to the trial treatment. Clear-cut temporal association and no other possible cause.

10.3 Definition of AE of special interest (AESI)

AESIs are events of scientific and medical interest specific to the further understanding of the MEDI4736 safety profile and require close monitoring and rapid communication by the investigator to the sponsor. The rapid reporting of these AESIs allows ongoing analysis of these events in order to characterize and understand them in association with the use of this investigational product.

AESIs may be **serious** (see section 11 for the definition of seriousness), or **non-serious**.

MEDI4736 belongs to a new class of anticancer therapies, called “checkpoint-inhibitors” that amplify antitumor immune responses by blocking inhibitory signaling pathway modulated by the co-inhibitory or co-stimulatory receptors, CTLA-4 and PD-1, expressed on T cells [80]. This class of IMP can have a wide spectrum of immune-mediated reactions that have been considered inflammatory in nature and can affect any organs of the body. Refer to the current version of the IB for further information.

10.3.1 Pneumonitis

Immune-mediated pneumonitis is characterized by inflammation focally or diffusely affecting the lung parenchyma that may be result of effects of checkpoint inhibitors against the normal lung parenchyma. Presentations of pneumonitis range from asymptomatic lung infiltrates to those that mimic severe bacterial pneumonia. For symptomatic patients, complaints and findings may include dyspnea, cough, tachypnea, pleuritic chest pain, and hypoxia.

In clinical studies with MEDI4736 monotherapy, 23 of 1’149 patients (2.0%) reported 24 serious and non-serious events (10 serious; 14 non-serious) of pneumonitis/interstitial lung disease across all doses and indications in 4 of the 5 open-label monotherapy studies [47].

Initial work-up should include high-resolution CT scan, ruling out infection, and pulse oximetry. Pulmonary consultation is highly recommended.

10.3.2 Hypersensitivity reactions

Hypersensitivity reactions as well as infusion-related reactions have been reported with anti-PD-L1 and anti-PD-1 therapy [81]. As with the administration of any foreign protein and/or other biologic agents, reactions following the infusion of mAbs can be caused by various mechanisms, including acute anaphylactic (IgE-mediated) and anaphylactoid reactions against the mAb, and serum sickness. Acute allergic reactions may occur, may be severe, and may result in death. Acute allergic reactions may include hypotension, dyspnea, cyanosis, respiratory failure, urticaria, pruritus, angioedema, hypotonia, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension, myalgia, vomiting and unresponsiveness.

In clinical studies with MEDI4736 as a monotherapy, the incidence of reported potential infusion-related reaction was low. Ten of 1,265 patients treated with MEDI4736 in 5 sponsored monotherapy studies reported 14 serious cases of infusion-related reactions, giving an overall frequency of 0.8%.

The potential risk of immune complex disease for MEDI4736 is theoretical based on the known risk associated with mAbs and other proteins. The incidence of MEDI4736 ADA-positive subjects in clinical studies is low, and hence the risk of immune complex disease is likely to be low.

10.3.3 Hepatic function abnormalities (hepatotoxicity)

Increased transaminases have been reported during treatment with anti-PD-L1/anti-PD-1 antibodies [81]. Inflammatory hepatitis has been reported in 3% to 9% of subjects treated with anti-

CTLA-4 monoclonal antibodies (e.g. ipilimumab). The clinical manifestations of ipilimumab-treated patients included general weakness, fatigue, nausea and/or mild fever and increased liver function tests such as AST, ALT, AP and/or total bilirubin. Across approximate 1,200 patients who have received MEDI4736 monotherapy 10 mg/kg q2w, 0.3% of subjects experienced an event of 'hepatitis'.

Hepatic function abnormality is defined as any increase in ALT or AST to greater than 3 × ULN and concurrent increase in total bilirubin to be greater than 2 × ULN. Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. Follow-up investigations and inquiries will be initiated promptly by the local investigator to determine whether the findings are reproducible and/or whether there is objective evidence that clearly supports causation by a disease (e.g. cholelithiasis and bile duct obstruction with distended gallbladder) or an agent other than the investigational product.

Cases where a patient shows an AST or ALT ≥ 3x ULN or total bilirubin ≥ 2x ULN may need to be reported as SAEs, 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.

Criteria for Hy's Law (FDA Guidance)

- The drug causes hepatocellular injury, generally shown by a higher incidence of 3 fold or greater elevations above the ULN of ALT or AST than the (non-hepatotoxic) control drug or placebo.
- Among trial patients showing such aminotransferase elevations, often with aminotransferases much greater than 3 x ULN, one or more also show elevation of serum total bilirubin to >2 x ULN, without initial findings of cholestasis (elevated serum AP).
- No other reason can be found to explain the combination of increased aminotransferases and total bilirubin, such as viral hepatitis A, B, or C; pre-existing or acute liver disease; or another drug capable of causing the observed injury.

Hepatic function abnormality in a patient receiving MEDI4736, with or without associated clinical manifestations, is required to be reported as "hepatic function abnormal" unless a definitive underlying diagnosis for the abnormality (e.g. cholelithiasis or bile duct obstruction) that is unrelated to investigational product has been confirmed.

- If the definitive underlying diagnosis for the abnormality has been established and is unrelated to MEDI4637, the decision to continue dosing of the patient will be based on the clinical judgment of the investigator.
- If no definitive underlying diagnosis for the abnormality is established, dosing of the patient must be interrupted immediately. Follow-up investigations and inquiries must be initiated by the investigational site without delay.

10.4 Reporting of AESI

AESIs in patients receiving MEDI4736 must be reported to SAKK CC as follows:

- Non-serious AESI: online, through the EDC system (www.sakk.ch/edc), by creating a new AE for the corresponsing patient, within 1 working day after knowledge of the event; the tick-box whether the event is an AESI must be checked.
- Serious AESI: by Fax, **within 24 hours** of knowledge of the event, using the SAE form **in case the AESI complies with the definition for seriousness** (see section 11).

The SAKK CC will forward each individual report to the coordinating investigator and to AstraZeneca within 1 working day after receipt from the site.

10.5 Drug-related AEs

Very common and common AEs related to cisplatin/docetaxel and MEDI4736 are presented in the tables below (see 10.5.1 and 10.5.2).

Please refer to the locally approved product information of cisplatin and docetaxel for exhaustive information concerning chemotherapy drug-related AEs (see e.g. http://www.swissmedicinfo.ch/) . Please note that the frequencies of AEs associated with MEDI4736 and summarized in the tables below may undergo changes as the number of patients being exposed to this investigational product is still small. **Always refer the most current IB version for an exhaustive list of AEs related to MEDI4736.**

10.5.1 Very common (> 10%)

SOC (CTCAE v4.03)	Cisplatin	Docetaxel	MEDI4736
Blood and lymphatic system disorders	Anemia	Anemia	
Infections and infestations		Pharyngitis, Other Infections, Rhinorrhea	
Immune system disorders		Anaphylactoid type reactions, Hypersensitivity reactions	
Investigations	White blood cell decreased, Platelet count decreased	Neutrophil count decreased, Platelet count decreased	
Ear and labyrinth disorders	Tinnitus, Hearing impaired		
Eye disorders		Watering eyes	
Gastrointestinal disorders	Nausea, Vomiting	Diarrhea, Nausea, Vomiting, Stomatitis	Diarrhea (G1/G2)
General disorders and administration site conditions		Fever, Flu like symptoms, Chills, Edema limbs	Fatigue
Metabolism and nutrition disorders		Anorexia	
Musculoskeletal and connective tissue disorders		Myalgia, Muscular weakness	
Nervous system disorders		Peripheral sensory neuropathy	
Psychiatric disorders		Insomnia	
Renal and urinary disorders	Urinary retention, Acute kidney injury		
Respiratory, thoracic and mediastinal disorders		Dyspnea	
Skin and subcutaneous tissue disorders		Alopecia, Erythema, Pruritus, Nail loss	Pruritus, Rash (G1/G2)

10.5.2 Common (1-10%)

SOC (CTCAE v4.03)	Cisplatin	Docetaxel	MEDI4736
Blood and lymphatic system disorders		Febrile neutropenia	Anemia
Cardiac disorders		Tachycardia	
Endocrine disorders			Hypertyroidism, Hypothyroidism
Eye disorders	Blurred vision	Conjunctivitis	
Gastrointestinal disorders		Constipation, Abdominal pain, Esophagitis, Dysphagia,	Nausea, Vomiting, Diarrhea

		Gastrointestinal disorders - Other (odynophagia)	
General disorders and administration site conditions		Injection site reaction	Fever, Asthenia
Infections and infestations		Oral candidiasis	
Investigations		Blood bilirubin increased, Alkaline phosphatase increased, Aspartate aminotransferase increased, Alanine aminotransferase increased	Aspartate aminotransferase increased, Alanine aminotransferase increased, GGT increased, Weight loss, Creatinine increased
Metabolism and nutrition disorders			Decreased appetite/ Anorexia (G1)
Musculoskeletal and connective tissue disorders		Arthralgia	Arthralgia, Myalgia
Nervous system disorders	Peripheral sensory neuropathy	Dysgeusia	Paresthesia
Psychiatric disorders		Depression	
Respiratory, thoracic and mediastinal disorders		Epistaxis	Pneumonitis, Dyspnea, Cough
Skin and subcutaneous tissue disorders		Dry skin	
Vascular disorders		Hypotension, hypertension	

10.5.3 Immune-related AEs (irAEs)

Based on the mechanism of action of MEDI4736 leading to T-cell activation and proliferation, there is the possibility of observing irAEs during the conduct of this trial. Potential irAEs include immune-mediated pneumonitis, enterocolitis, dermatitis, hepatitis/hepatotoxicology, endocrinopathies, neuropathy /neuromuscular toxicity, nephritis, pancreatitis and myocarditis. Patients should be monitored for signs and symptoms of irAEs. In the absence of an alternate etiology (e.g. infection or PD/relapse) signs or symptoms of these events should be considered to be immune-related.

10.5.4 Hypersensitivity and serious allergic reactions

These events include infusion-related reactions, anaphylaxis/serious allergic reactions and immune complexe disease.

10.6 Safety parameters

Renal function:	Serum creatinine or calculated creatinine clearance (according to the formula of Cockcroft-Gault, see Appendix 3)
Liver function:	AST/ALT
Hematological function:	Hemoglobin, absolute neutrophils count, platelets count
Metabolic function:	Sodium (Na), potassium (K), magnesium (Mg)
Cardiovascular function:	Blood pressure, 12-lead ECG
Vital signs:	During MEDI4736 infusion - temperature, blood pressure, pulse rate, and respiratory rate

10.7 Dose modifications and supportive treatment during treatment with cisplatin/docetaxel

Refer also to the locally approved product information of cisplatin and docetaxel (see e.g. http://www.swissmedicinfo.ch/).

10.7.1 Hematological adverse events

Neutrophil count decreased	**Cisplatin**	**Docetaxel**
G1 and G2 (≥ 1.0 x 10^9/L)	No change.	
G3 or G4 (< 1.0 x 10^9/L)	Delay for a maximum of 2 weeks until recovery to < G3; blood counts have to be measured twice weekly until recovery. Permanently discontinue chemotherapy if not recovered within 2 weeks.	

Platelet count decreased		**Cisplatin**	**Docetaxel**
< 100 x 10^9/L prior each cycle		Delay for a maximum of 2 weeks until recovery to > 100 x 10^9/L. Blood counts have to be measured twice weekly until recovery. Permanently discontinue chemotherapy if not recovered within 2 weeks (proceed to MEDI4736 therapy if no PD and if clinically indicated).	
G3 (< 50 x 10^9/L) or G4 (< 25 x 10^9/L) during the cycle	First occurrence	No change.	Reduce dose to 55 mg/m2.
	Second occurrence	No change.	Reduce dose to 30 mg/m^2.

10.7.2 Metabolic/laboratory adverse events

In case of abnormal liver function or renal insufficiency prior each chemotherapy cycle, the following dose modifications must be applied.

Of note: Every attempt should be made to document the etiology of the liver function impairment. **Metastatic disease to the liver needs to be excluded**.

AST or ALT or AP or bilirubin	**Cisplatin**	**Docetaxel**
G1	No change.	
G2	No change.	Reduce dose to 55 mg/m^2.
G3 or G4	Delay for a maximum 2 weeks until resolution to ≤ G2 and then restart with docetaxel dose reduced to 55 mg/m^2. Permanently discontinue chemotherapy if not resolved within 2 weeks.	

Renal insufficiency	**Cisplatin**	**Docetaxel**
Creatinine clearance < 60 ml/min prior each cycle	Stop cisplatin and replace by carboplatin AUC6, acc. to Calvert formula (see 9.2).	No change.

10.7.3 Ear and labyrinth disorders

Hearing impairment	**Cisplatin**	**Docetaxel**
G1 (audiogram only)	No change.	
≥ G2	Stop cisplatin and replace by carboplatin AUC6, acc. to Calvert formula (see 9.2).	No change.

10.7.4 Nervous system disorders

Sensory / peripheral neuropathy		**Cisplatin**	**Docetaxel**
G1		No change.	
G2	First occurrence	Stop cisplatin and replace by carboplatin AUC6, acc. to Calvert formula (see 9.2).	No change.
	In case of persistence at next administration	Stop cisplatin and replace by carboplatin AUC6, acc. to Calvert formula (see 9.2).	Reduce dose to 55 mg/m^2.
≥ G3		Permanently discontinue chemotherapy.	

10.7.5 Gastrointestinal disorders

Nausea and vomiting		**Cisplatin**	**Docetaxel**
G1 or G2		No change.	
G3	First occurrence	No change.	No change.
	Second occurrence	Stop cisplatin and replace by carboplatin AUC6, acc. to Calvert formula (see 9.2).	Continue with the reduced dose of 55 mg/m^2.

Diarrhea		**Cisplatin**	**Docetaxel**
G1 or G2		No change.	
G3	First occurrence	No change.	No change.
	Second occurrence	No change.	Continue with the reduced dose of 55 mg/m^2.

10.7.6 Docetaxel-induced hypersensitivity or anaphylactic type reactions

Anaphylactic type reactions, hypersensitivity reactions		**Cisplatin**	**Docetaxel**	**Supportive treatment**
G1		No change.	Decrease infusion rate until recovery to Grade 0. Then complete infusion with initial infusion rate.	
G2		No change.	Interrupt infusion. Re-start infusion after recovery to Grade 0 at a slower rate and then increase incrementally to the initial rate.	Give i.v. antihistamine[1] and i.v. corticosteroids[2]. At subsequent cycles, antihistamines and steroids will be given i.v. 1 hour before infusion in addition to the premedication.
G3	First occurrence	No change.	Interrupt infusion. Once all signs and/or symptoms of hypersensitivity reaction disappear, infusion may be resumed within 24 hours from the interruption, if medically appropriate, and whenever possible. Reiteration of the premedication regimen is only recommended when docetaxel is re-infused more than 3 hours after the interruption.	Give i.v. antihistamine[1] and corticosteroids[2]. Add epinephrine[3] or broncho-dilatators and/or i.v. fluids, macro-molecules if indicated. At the subsequent cycles, dexamethasone will be given at 20 mg orally 24, 18, 13, 7 and 1 hour before docetaxel infusion. Additionally diphenhydramine (or equivalent) will be given at 50 mg i.v. 1 hr before docetaxel infusion.

	Second occurrence	Permanently discontinue chemotherapy.	
G4		Permanently discontinue chemotherapy.	

[1]Antihistamines: Dexchlorphenidramine (Polaramine®) 5-10 mg i.v. or clemastine (Tavegyl®) 2 mg i.v. or diphenhydramine (Benadryl®) 25-50 mg i.v. or promethazine (Phenergan®) 50-100 mg i.v.

[2]Corticosteroids: Dexamethason or equivalent of 5-10 mg i.v.

[3]Epinephrine: Administered at 1:1'000 dilution (0.01 ml/kg with a maximum dose of 0.5 ml s.c. repeated every 20 minutes as necessary).

10.7.7 Fluid retention

Peripheral edemas and/or pleural effusions	**Cisplatin**	**Docetaxel**	**Supportive measures**
G1	No change		
G2	The clinical tolerance of the therapy by the patient, the overall tumor response and the medical judgment of the investigator will determine if it is in the patient's best interest to continue or to discontinue the treatment.		Furosemid (20-40 mg once daily p.o.) should be started when signs and/or symptoms of fluid retention are observed, including weight gain G2 not otherwise explained. The addition of potassium and magnesium may be useful.
≥ G3	Permanently discontinue chemotherapy		

In case of a pleural effusion or ascites appearing or increasing during the treatment, the cytological examination and concomitant signs of disease progression or of peripheral fluid retention should allow deciding whether the effusion is related to the disease or the trial drugs. In case of difficulty to determine, the treatment should be continued until clear evidence of disease progression in other organs can be documented.

10.7.8 Other adverse events

Other AEs ≥ G3 (except alopecia) should be managed symptomatically when possible.

Other AEs	**Cisplatin**	**Docetaxel**
G3	Delay for a maximum of 2 weeks until resolved to ≤ G1, then, if medically appropriate, reduce docetaxel to 55 mg/m^2 (no further dose reduction is foreseen).	
G4	Permanently discontinue chemotherapy.	

10.8 Toxicity management guidelines during MEDI4736 therapy

For AEs that are considered at least partly due to administration of MEDI4736 the following dose adjustment guidance may be applied:

- Treat each of the AEs with maximum supportive care (including holding the agent suspected of causing the toxicity where required),
- If the symptoms promptly resolve with supportive care, consideration should be given to continuing MEDI4736 along with appropriate continuing supportive care,
- All treatment interruptions should be documented with clear reasoning and documentation of the approach taken,
- MEDI4736 must not be delayed for longer than 2 weeks during neoadjuvant treatment, and 6 weeks during adjuvant treatment.

Management guidelines for AEs associated with MEDI4736 (overall management and AE-specific management), are detailed in the tables below. Refer also to the most current version of the IB.

10.8.1 Immune-related reactions associated with MEDI4736

Please also consider the most current version of the IB.

IrAEs (Overall management for toxicities not noted below)	
Dose Modifications	**Toxicity Management**
Drug administration modifications of MEDI4736 will be made to manage potential irAEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v4.03. In addition to the criteria for permanent discontinuation of MEDI4736 based on severity/Grade (table below), permanently discontinue MEDI4736 for the following conditions: • Inability to reduce corticosteroid to a dose of ≤10 mg of prednisone per day (or equivalent) **within 12 weeks** after last dose of MEDI4736, • Recurrence of a previously experienced G3 treatment-related AE following resumption of dosing. G1 No dose modification G2 Hold MEDI4736 dose until G2 resolution to ≤ G1 • If toxicity worsens then treat as G3 or G4 • If toxicity improves to baseline then treat at next scheduled treatment date • Once event stabilizes to ≤ G1 and corticosteroid is reduced to a dose ≤10 mg of prednisone per day (or equivalent) then MEDI4736 treatment can be resumed at the next scheduled dose G3 Depending on the individual toxicity, may permanently discontinue MEDI4736. Please refer to guidelines below G4 Permanently discontinue MEDI4736 Note: For G3 and above asymptomatic amylase or lipase levels hold MEDI4736 and if complete work up shows no evidence of pancreatitis, may continue or resume treatment.	It is recommended that management of irAEs follow the guidelines presented in this table: – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g. disease progression, concomitant medications, infections, etc.). – In the absence of a clear alternative etiology, all events should be considered potentially immune related and **discussed with the coordinating investigators**. – Symptomatic and topical therapy should be considered for low-grade (G1/G2, unless otherwise specified) irAEs. – For persistent (greater than 3 to 5 days) low-grade (G2) or severe (≥G3) irAEs, promptly start prednisone p.o. 1-2 mg/kg/day or i.v. equivalent. – If symptoms recur or worsen during corticosteroid tapering, increase the corticosteroid dose (prednisone dose, e.g. up to 2-4 mg/kg/day or i.v equivalent) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate. – More potent immunosuppressives, such as TNF antagonist class (e.g. infliximab) or mycophenolate, etc. (refer to individual sections of the irAE management for specific type of immunosuppressive) should be considered for events not responding to systemic steroids **after discussion with the coordinating investigators**. – Discontinuation of MEDI4736 is not mandated for G3/G4 inflammatory reactions attributed to local tumour response (e.g. inflammatory reaction at sites of metastatic disease, lymph nodes, etc.). Continuation of MEDI4736 in this situation should be based upon a benefit/risk analysis for that patient.

Grade (CTCAE v4.03)	Dose Modifications	Toxicity Management
Pneumonitis / Interstitial lung disease (ILD)		
Any Grade		– Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests including other diagnostic procedures as described below – Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up and high-resolution CT scan
G1 (Asymptomatic, clinical or diagnostic observations only, intervention not indicated)	No dose modification required. However, consider holding MEDI4736 dosing as clinically appropriate and during diagnostic work-up for other etiologies	For G1 (radiographic changes only) – Monitor and closely follow up in 2-4 days for clinical symptoms, pulse oximetry (resting and exertion) and laboratory work-up and then as clinically indicated – Consider pulmonary and infectious disease consult
G2 (Symptomatic, medical intervention indicated, limiting instrumental ADL)	Hold MEDI4736 dose until resolution to ≤ G1 • If toxicity worsens then treat as G3 or G4 • If toxicity improves to baseline then the decision to reinitiate study drug/regimen at next scheduled treatment date will be based upon treating physician's clinical judgment • Once event stabilizes to ≤ G1 and corticosteroid is reduced to a dose ≤10 mg of prednisone per day (or equivalent) then MEDI4736 treatment can be resumed at the next scheduled dose	For G2 (mild to moderate new symptoms) – Monitor symptoms daily and consider hospitalization – Promptly start systemic steroids (e.g. prednisone 1-2 mg/kg/day or i.v. equivalent) – Re-imaging as clinically indicated – If no improvement within 3-5 days, additional workup should be considered and prompt treatment with i.v. methylprednisolone 2-4 mg/kg/day started – If still no improvement within 3-5 days despite i.v. methylprednisone at 2-4 mg/kg/day, promptly start immunosuppressive therapy (e.g. infliximab at 5 mg/kg every 2 weeks). Caution: Important to rule out sepsis and refer to infliximab label for general guidance before using infliximab – Once improving, gradually taper steroids and consider prophylactic antibiotics, antifungal or anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation)[1] – Consider pulmonary and infectious disease consult – Consider as necessary discussing with coordinating investigators

[1] ASCO Educational Book 2015; Michael Pestow MD; "Managing Immune Checkpoint Blocking Antibody Side Effects", Section on Hepatotoxicity, pp 78

Grade (CTCAE v4.03)	Dose Modifications	Toxicity Management
G3 or G4 (G3: severe symptoms; limiting self-care ADL; oxygen indicated; G4: life threatening respiratory compromise, urgent intervention indicated, e.g. tracheostomy or intubation)	Permanently discontinue MEDI4736	For G3 or G4 (severe or new symptoms, new/worsening hypoxia, life threatening) - Promptly initiate empiric i.v. methylprednisolone 1 to 4 mg/kg/day or equivalent - Obtain pulmonary and infectious disease consult - Hospitalize the patient - Supportive care (oxygen, etc.) - If no improvement within 3-5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy (e.g. infliximab at 5 mg/kg every 2 weeks dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab - Once improving, gradually taper steroids and consider prophylactic antibiotics, antifungals and in particular, anti-PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation)
Diarrhea / Enterocolitis		
Any Grade		- Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs and ileus) - Patients should be thoroughly evaluated to rule out any alternative etiology (e.g. disease progression, other medications, infections including testing for clostridium difficile toxin, etc.) - Steroids should be considered in the absence of clear alternative etiology, even for low-grade events, in order to prevent potential progression to higher grade event - Use analgesics carefully; they can mask symptoms of perforation and peritonitis
G1 (stool frequency of <4 over baseline per day)	No dose modification	- Close monitoring for worsening symptoms - Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (e.g. American Dietetic Association colitis diet), and loperamide. Use of probiotics as per treating physician's clinical judgment
G2 (stool frequency of 4-6 over baseline per day)	Hold MEDI4736 until resolution to ≤G1 • If toxicity worsens then treat as G3 or G4 • If toxicity improves to baseline then treat at next scheduled treatment date • Once event stabilizes to ≤ G1 and corticosteroid is reduced to a dose ≤10 mg	- Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (e.g. American Dietetic Association colitis diet), and loperamide and/or budesonide - Promptly start prednisone 1 to 2 mg/kg/day or i.v. equivalent - If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day or i.v. equivalent, gastrointestinal consult should be obtained for

Grade (CTCAE v4.03)	Dose Modifications	Toxicity Management
	of prednisone per day (or equivalent) then MEDI4736 treatment can be resumed at the next scheduled dose	consideration of further workup such as imaging and/or colonoscopy to confirm colitis and rule out perforation, and prompt treatment with i.v. methylprednisolone 2-4 mg/kg/day started – If still no improvement within 3-5 days despite 2-4 mg/kg i.v. methylprednisolone, promptly start immunosuppressives (e.g. infliximab at 5 mg/kg once every 2 weeks[2]). **Caution**: Important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab – Consult coordinating investigators if no resolution to ≤ G1 in 3-4 days – Once improving, gradually taper steroids and consider prophylactic antibiotics, antifungals and anti-PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])
G3 or G4 (G3: stool frequency of ≥7 over baseline per day; G4: life threatening consequences)	Permanently discontinue MEDI4736	– Promptly initiate empiric i.v. methylprednisolone 2 to 4 mg/kg/day or equivalent – Monitor stool frequency and volume and maintain hydration – Urgent gastrointestinal consult and imaging and/or colonoscopy as appropriate – If still no improvement within 3-5 days of i.v. methylprednisolone 1 to 4 mg/kg/day or equivalent, promptly start further immunosuppressives e.g. (infliximab at 5 mg/kg once every 2 weeks) – Caution: Ensure gastrointestinal consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab – Once improving, gradually taper steroids and consider prophylactic antibiotics, antifungals and anti-PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])
Hepatitis (Elevated liver function tests (LFT))		
Infliximab should not be used for management of immune-related hepatitis		
Any Grade		– Monitor and evaluate liver function test: AST, ALT, AP and total bilirubin (TB) – Evaluate for alternative etiologies (e.g. viral hepatitis, disease progression, concomitant medications)
G1 (AST or ALT > ULN to 3 x ULN and/or TB > ULN to 1.5 x ULN)	No dose modification If it worsens, treat as G2 event	– Continue LFT monitoring per protocol

[2] ASCO Educational Book 2015; Michael Pestow MD; "Managing Immune Checkpoint Blocking Antibody Side Effects", Section on Diarrhea/Colitis, pp. 77

Grade (CTCAE v4.03)	Dose Modifications	Toxicity Management
G2 (AST or ALT > 3 to 5 x ULN and/or TB > 1.5-3 x ULN)	Hold MEDI4736 dose until resolution to ≤ G1 • If toxicity worsens then treat as G3 or G4 • If improves to baseline then treat at next scheduled treatment date • Once event stabilizes to ≤ G1 and corticosteroid is reduced to a dose ≤10 mg of prednisone per day (or equivalent) then MEDI4736 treatment can be resumed at the next scheduled dose	– Regular and frequent checking of LFTs (e.g. every 1-2 days) until elevations of these are improving or resolved – If no resolution to ≤ G1 in 1-2 days, discuss with coordinating investigators. – If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1-2 mg/kg/day or i.v. equivalent – If still no improvement within 3-5 days despite 1-2 mg/kg/day of prednisone or i.v. equivalent, consider additional workup and prompt treatment with i.v. methylprednisolone 2-4 mg/kg/day started – If still no improvement within 3-5 days despite 2-4 mg/kg/day of i.v. methylprednisolone, promptly start immunosuppressives (mycophenolate mofetil at 500 mg every 12 hours)[3] . Discuss with coordinating investigators if mycophenolate mofetil is not available. **Infliximab should NOT be used** – Once improving, gradually taper steroids and consider prophylactic antibiotics, antifungals and anti-PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])
G3 (AST or ALT > 5-20 x ULN and/or TB > 3-10 x ULN)	For elevations in transaminases ≤ 8 × ULN, or elevations in bilirubin ≤ 5 × ULN: -Hold MEDI4736 dose until resolution to ≤ G1 or baseline -Resume MEDI4736 administration at the next scheduled dose if elevations down-grade ≤ G1 or baseline within 14 days Permanently discontinue MEDI4736 if the elevations do not down-grade to ≤ G1 or baseline within 14 days For elevations in transaminases > 8 × ULN or elevations in bilirubin > 5 × ULN, discontinue MEDI4736 Permanently discontinue MEDI4736 for any case meeting Hy's law criteria (ALT > 3x ULN + bilirubin > 2x ULN without initial findings of cholestasis (i.e. elevated AP) and in the absence of any alternative cause[4]	For G3 or G4 AST or ALT and/or TB elevation: – Promptly initiate empiric i.v. methylprednisolone at 1 to 4 mg/kg/day or equivalent – If still no improvement within 3-5 days despite 1 to 4 mg/kg/day methylprednisolone i.v. or equivalent, promptly start treatment with immunosuppressive therapy (mycophenolate mofetil at 500 mg every 12 hours) Discuss with coordinating investigators if mycophenolate is not available. **Infliximab should NOT be used** – Hepatology consult, abdominal workup, and imaging as appropriate – Once improving, gradually taper steroids and consider prophylactic antibiotics, antifungals and anti-PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])

[3] ASCO Educational Book 2015; Michael Pestow MD; "Managing Immune Checkpoint Blocking Antibody Side Effects", Section on Hepatotoxicity, pp. 78
[4] FDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation

Grade (CTCAE v4.03)	Dose Modifications	Toxicity Management
G4 (AST or ALT > 20 x ULN and/or TB > 10 x ULN)	Permanently discontinue MEDI4736	
Nephritis or Renal dysfunction (Elevated serum creatinine)		
Any Grade		– Consult with nephrologist – Monitor for signs and symptoms that may be related to changes in renal function (e.g. routine urinalysis, elevated serum blood urea nitrogen (BUN) and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, proteinuria, etc.) – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g. disease progression, infections, etc.) – Steroids should be considered in the absence of clear alternative etiology even for low-grade events (G2), in order to prevent potential progression to higher grade event
G1 (Serum creatinine > 1-1.5 x baseline; > ULN to 1.5 x ULN)	No dose modification	– Monitor serum creatinine weekly and any accompanying symptom – If creatinine returns to baseline, resume its regular monitoring per study protocol – If it worsens, depending on the severity, treat as G2 or G3 or G4 – Consider symptomatic treatment including hydration, electrolyte replacement, diuretics, etc.
G2 (Serum creatinine > 1.5-3.0 x baseline; > 1.5-3 x ULN)	Hold MEDI4736 until resolution to ≤ G1 • If toxicity worsens then treat as G3 or G4 • If toxicity improves to baseline then treat at next scheduled treatment date • Once event stabilizes to ≤ G1 and corticosteroid is reduced to a dose ≤10 mg of prednisone per day (or equivalent) then MEDI4736 treatment can be resumed at the next scheduled dose	– Consider symptomatic treatment including hydration, electrolyte replacement, diuretics, etc. – Carefully monitor serum creatinine every 2-3 days and as clinically warranted – Consult nephrologist and consider renal biopsy if clinically indicated – If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day or i.v. equivalent – If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day or i.v. equivalent, additional workup should be considered and prompt treatment with i.v. methylprednisolone at 2-4 mg/kg/day started – Once improving gradually taper steroids and consider prophylactic antibiotics, antifungals and anti-PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) – When event returns to baseline, resume MEDI4736 and routine serum creatinine monitoring per study protocol

Grade (CTCAE v4.03)	Dose Modifications	Toxicity Management
G3 or G4 (G3: Serum creatinine > 3 x baseline; > 3-6 x ULN G4: Serum creatinine > 6 x ULN)	Permanently discontinue MEDI4736	– Carefully monitor serum creatinine on daily basis – Consult nephrologist and consider renal biopsy if clinically indicated – Promptly start prednisone 1 to 2 mg/kg/day or i.v. equivalent – If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day or i.v. equivalent, additional workup should be considered and prompt treatment with i.v. methylprednisolone 2-4 mg/kg/day started – Once improving, gradually taper steroids and consider prophylactic antibiotics, antifungals and anti-PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]
Rash (excluding Bullous skin formations)		
(Please refer to CTCAE version 4.03 for definition of severity/Grade depending on type of skin rash)		
Any Grade		Monitor for signs and symptoms of dermatitis (rash and pruritus) **IF THERE IS ANY BULLOUS FORMATION, THE COORDINATING INVESTIGATORS SHOULD BE CONTACTED **AND MEDI4736 DISCONTINUED****
G1	No dose modification	– Consider symptomatic treatment including oral antipruritics (e.g. diphenhydramine or hydroxyzine) and topical therapy (e.g. urea cream)
G2	For persistent (> 1-2 weeks) G2 events, hold scheduled MEDI4736 until resolution to ≤ G1 or baseline • If toxicity worsens then treat as G3 • If toxicity improves then resume administration at next scheduled dose • Once event stabilizes to ≤ G1 and corticosteroid is reduced to a dose ≤10 mg of prednisone per day (or equivalent) then MEDI4736 treatment can be resumed at the next scheduled dose	– Obtain dermatology consult – Consider symptomatic treatment including oral antipruritics (e.g. diphenhydramine or hydroxyzine) and topical therapy (e.g. urea cream) – Consider moderate-strength topical steroid – If no improvement of rash/skin lesions occurs within 3-5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, discuss with coordinating investigators and promptly start systemic steroids prednisone 1-2 mg/kg/day or i.v. equivalent – Consider skin biopsy if persistent for > 1-2 weeks or recurs
G3	Hold MEDI4736 until resolution to ≤ G1 or baseline If temporarily holding the MEDI4736 does not provide improvement of the G3 skin rash to ≤ G1 or baseline within 30 days, then permanently discontinue MEDI4736	For G3 or G4: – Consult dermatology – Promptly initiate empiric i.v. methylprednisolone 1 to 4 mg/kg/day or equivalent – Consider hospitalization – Monitor extent of rash [Rule of Nines] – Consider skin biopsy (preferably more than 1) as clinically feasible. CONT.
G4	Permanently discontinue MEDI4736	

Grade (CTCAE v4.03)	Dose Modifications	Toxicity Management
		– Once improving, gradually taper steroids and consider prophylactic antibiotics, antifungals and anti-PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) – Discuss with coordinating investigators
Endocrinopathy (e.g. hyperthyroidism, hypothyroidism, hypopituitarism, adrenal insufficiency, etc.)		
(Depending on the type of endocrinopathy, refer to CTCAE version 4.03 for defining the CTCAE severity/Grade)		
Any Grade		– Consult endocrinologist – Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, hypotension and weakness – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g. disease progression including brain metastases, infections, etc.) – Monitor and evaluate thyroid function tests: TSH, free T_3 and free T_4 and other relevant endocrine labs depending on suspected endocrinopathy – If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g. thyroiditis, pancreatitis, hypophysitis, diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing
G1	No dose modification	For G1: (including those with asymptomatic thyroid stimulating hormone (TSH) elevation) – Monitor patient with appropriate endocrine function tests – If TSH < 0.5x LLN, or TSH > 2x ULN or consistently out of range in 2 subsequent measurements, include FT4 at subsequent cycles as clinically indicated and consider endocrinology consult
G2	For G2 endocrinopathy other than hypothyroidism, hold MEDI4736 dose until subject is clinically stable • If toxicity worsens then treat as G3 or G4 • If toxicity improves to baseline then treat at next scheduled treatment date • Once event stabilizes to ≤ G1 and corticosteroid is reduced to a dose ≤10 mg of prednisone per day (or equivalent) then MEDI4736 treatment can be resumed at	For G2: (including those with symptomatic endocrinopathy) – Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids – Initiate hormone replacement as needed for management – Evaluate endocrine function, and as clinically indicated, consider pituitary scan – For patients with abnormal endocrine work up, except for those with isolated hypothyroidism, consider short-term, corticosteroids (e.g. 1-2 mg/kg/day methylprednisolone or i.v. equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g. levothyroxine, hydrocortisone, or sex hormones). CONT.

Grade (CTCAE v4.03)	Dose Modifications	Toxicity Management
	the next scheduled dose Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with MEDI4736 on the following conditions: 1. the event stabilizes and is controlled 2. the subject is clinically stable as per investigator or treating physician's clinical judgement 3. doses of prednisone are ≤ 10 mg/day or equivalent	– Once improving, gradually taper steroids and consider prophylactic antibiotics, antifungals and anti-PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) – For patients with normal endocrine work up (lab or MRI scans), repeat labs/MRI as clinically indicated
G3 or G4	For G3 or G4 endocrinopathy other than hypothyroidism, hold MEDI4736 dose until endocrinopathy symptom(s) are controlled Resume MEDI4736 administration if control-led at the next scheduled dose MEDI4736 treatment can be resumed at the next scheduled dose once event stabilizes to ≤ G1 and corticosteroid is reduced to a dose ≤10 mg of prednisone per day (or equivalent)	For G3 or G4: – Consult endocrinologist – Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids – Promptly initiate empiric i.v. methylprednisolone 1 to 2 mg/kg/day or equivalent – Administer hormone replacement therapy as necessary – For adrenal crisis, severe dehydration, hypotension, or shock: immediately initiate intravenous corticosteroids with mineralocorticoid activity – Once improving, gradually taper immunosuppressive steroids and consider prophylactic antibiotics, antifungals and anti-PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) – Discuss with coordinating investigators
Immune mediated Neurotoxicity **(to include but not limited to limbic encephalitis, autonomic neuropathy; *excluding Myasthenia Gravis and Guillain-Barre*)**		
Depending on the type of neurotoxicity , refer to CTCAE version 4.03 for defining the severity/Grade		
Any Grade		– Patients should be evaluated to rule out any alternative etiology (e.g. disease progression, infections, metabolic syndromes and medications, etc.) – Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness) – Consider appropriate diagnostic testing (e.g. electromyogram and nerve conduction investigations) – Symptomatic treatment with neurological consult as appropriate
G1	No dose modifications	See "Any Grade" recommendations above.

Grade (CTCAE v4.03)	Dose Modifications	Toxicity Management
G2	For acute motor neuropathies or neurotoxicity, hold MEDI4736 dose until resolution to ≤ G1 For sensory neuropathy/neuropathic pain, consider holding MEDI4736 dose until resolution to ≤ G1 • If toxicity worsens then treat as G3 or G4 • If toxicity improves to baseline then treat at next scheduled treatment date • Once event stabilizes to ≤ G1 and corticosteroid is reduced to a dose ≤10 mg of prednisone per day (or equivalent) then MEDI4736 treatment can be resumed at the next scheduled dose	– Discuss with the coordinating investigators – Obtain neurology consult – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g. gabapentin, duloxetine, etc.) – Promptly start systemic steroids prednisone 1-2 mg/kg/day or i.v. equivalent – If no improvement within 3-5 days despite 1-2 mg/kg/day prednisone or i.v. equivalent consider additional workup and promptly treat with additional immunosuppressive therapy (e.g. IVIgG)
G3	Hold MEDI4736 dose until resolution to ≤ G1 Permanently discontinue MEDI4736 if G3 irAE does not resolve to ≤ G1 within 30 days.	For G3 or G4: – Discuss with coordinating investigators – Obtain neurology consult – Consider hospitalization – Promptly initiate empiric i.v. methylprednisolone 1 to 2 mg/kg/day or equivalent – If no improvement within 3-5 days despite i.v. corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (e.g. IVIgG) – Once stable, gradually taper steroids
G4	Permanently discontinue MEDI4736	
Immune-mediated peripheral neuromotor syndromes, such as Guillain-Barre and Myasthenia Gravis		
Any Grade		– The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations which can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms which may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability – Patients should be evaluated to rule out any alternative etiology (e.g. disease progression, infections, metabolic syndromes and medications, etc.). It should be noted that the diagnosis of immune-mediated peripheral neuromotor

Grade (CTCAE v4.03)	Dose Modifications	Toxicity Management
		syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult – Neurophysiologic diagnostic testing (e.g. electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation Important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IVIgG and followed by plasmapheresis if not responsive to IVIgG
G1	No dose modification	– Discuss with the coordinating investigators – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above – Obtain a neurology consult unless the symptoms are very minor and stable
G2	Hold MEDI4736 dose until resolution to ≤ G1 Permanently discontinue MEDI4736 if it does not resolve to ≤ G1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability	– Discuss with the coordinating investigators – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above – Obtain a neurology consult – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g. gabapentin, duloxetine, etc.) *MYASTHENIA GRAVIS* o Steroids may be successfully used to treat Myasthenia Gravis. Important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient o If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis *GUILLAIN-BARRE:* – Important to consider here that the use of steroids as the primary treatment of

Grade (CTCAE v4.03)	Dose Modifications	Toxicity Management
		Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IVIgG and followed by plasmapheresis if not responsive to IVIgG
G3	Hold MEDI4736 dose until resolution to ≤ G1 Permanently discontinue MEDI4736 if G3 irAE does not resolve to ≤ G1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability	For severe or life threatening (G3 or G4) events: - Discuss with coordinating investigators - Recommend hospitalization - Monitor symptoms and obtain neurological consult *MYASTHENIA GRAVIS* o Steroids may be successfully used to treat Myasthenia Gravis. It should typically be administered in a monitored setting under supervision of a consulting neurologist o Patients unable to tolerate steroids may be candidates for treatment with plasmapharesis or IVIgG o If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis *GUILLAIN-BARRE*: Important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IVIgG and followed by plasmapheresis if not responsive to IVIgG
G4	Permanently discontinue MEDI4736	

10.8.2 Infusion-related reactions associated with MEDI4736

Please also consider the most current version of the IB.

Grade (CTCAE v4.03)	Dose Modifications	Toxicity Management
Any Grade		- Management per institutional standard at the discretion of investigator - Monitor patients for signs and symptoms of infusion-related reactions (e.g. fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, skin rashes, etc.) and anaphylaxis (e.g. generalized urticaria, angioedema, wheezing, hypotension, tachycardia, etc.)
G1	The infusion rate of MEDI4736 may be decreased by 50% or temporarily interrupted until resolution of the event	- Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator - Consider premedication per institutional standard prior to subsequent doses
G2	The infusion rate of MEDI4736 may be decreased 50% or temporarily interrupted until resolution of the event Subsequent infusions may be given at 50% of the initial infusion rate	
G3/4	Permanently discontinue MEDI4736	- Manage severe infusion-related reactions per institutional standards (e.g. intramuscular epinephrine, followed by i.v. diphenhydramine and ranitidine, and i.v. glucocorticoid)

10.8.3 Non-immune mediated reactions associated with MEDI4736

Please also consider the most current version of the IB.

Grade (CTCAE v4.03)	Dose Modifications	Toxicity Management
Any Grade	Note: dose modifications are not required for AEs not deemed to be related to study treatment (i.e. events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant	Treat accordingly as per institutional standard
G1	No dose adjustment	Treat accordingly as per institutional standard
G2	Hold MEDI4736 until resolution to ≤ G1 or baseline	Treat accordingly as per institutional standard

Grade (CTCAE v4.03)	Dose Modifications	Toxicity Management
G3	Hold MEDI4736 until resolution to ≤ G1 or baseline For AEs that down-grade to ≤ G2 within 7 days or resolve to ≤ G1 or baseline within 14 days, resume MEDI4736 administration at next scheduled dose. Otherwise, discontinue MEDI4736	Treat accordingly as per institutional standard
G4	Discontinue MEDI4736 (Note for G4 labs: decision to discontinue would be based on accompanying clinical signs/symptoms and as per treating investigator's clinical judgment and in consultation with the coordinating Investigators)	Treat accordingly as per institutional standard

11 SAFETY REPORTING

11.1 Definition of serious adverse event (SAE)

11.1.1 SAEs during trial treatment

SAE to be reported are **any of the events listed in the table below** and occurring between registration and up to 90 days after the last dose of MEDI4736 or until the initiation of alternative anticancer therapy. In case trial treatment is interrupted before any dose of MEDI4736 is administered, SAE are to be reported until 30 days from last dose of chemotherapy:

Criteria fulfilling the condition for a SAE

SAE	**Comments**
Fatal	All events resulting in death.
Life-threatening	The patient was at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more serious form, might have caused death.
Requires inpatient hospitalization (> 24 hours)	Events not considered to be SAE are hospitalizations > 24 hours and occurring under the following circumstances: - elective surgery (planned before entry into the trial), - protocol-related treatments, procedures or monitoring, - social reasons (e.g. in rehabilitation home), - disease progression.
Prolongs hospitalization	Prolongation of an existing hospitalization.
Disabling	Includes persistent or relevant disability or incapacity.
Secondary malignancy	Any new malignancy other than a relapse of the current tumor.
Congenital anomaly	Birth defect in neonate/infant or stillbirth.
Other medically significant condition	Important events that are not immediately life-threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above.

11.1.2 SAEs after the end of trial treatment

During the follow-up phase (starting 90 days after the last dose of MEDI4736; or 30 days after the last dose of chemotherapy in case trial treatment was interrupted before any dose of MEDI4736 was administered), the following events have to be reported as SAE:

SAE	**Comments**
Fatal	Defined as above, but only events **possibly, probably or definitely** related to (late effects of) trial treatment/procedure.
Life-threatening	Defined as above, but only events **possibly, probably or definitely** related to (late effects of) trial treatment.
Disabling	Defined as above, but only events **possibly, probably or definitely** related to (late effects of) trial treatment.
Secondary malignancy	Any new malignancy other than a relapse of the current tumor.
Congenital anomaly	Birth defect in neonate/infant or stillbirth.
Other medically significant condition	Defined as above, but only events **possibly, probably or definitely** related to (late effects of) trial treatment.

11.2 Definition of serious adverse reaction (SAR)

SARs are all SAEs considered to be possibly, probably or definitely related to the trial treatment.

11.3 Definition of suspected unexpected serious adverse reactions (SUSARs)

SUSARs are serious adverse reactions that are related to medication and assessed as unexpected on the basis of the applicable product information (cisplatin/docetaxel) or the IB (MEDI4736).

11.4 Reporting of individual SAEs by the investigator

Any SAE must be reported by submitting the completed **initial report** section of the trial-specific SAE form **within 24 hours** of becoming aware of the event. This form can be downloaded from the SAKK website (www.sakk.ch → Members → Trials → Lung Cancer → SAKK 16/14 → CRFs).

Reporting is done by sending the SAE form by fax to:

Fax: +41 31 508 41 42

The SAE outcome must be reported within 2 weeks after initial report by submitting the **follow-up** report (e.g. initial SAE form, updated with follow-up information) to the SAKK CC by fax. In case the SAE is reported as ongoing after 14 days, the follow-up report has to be submitted again with the final outcome. 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.

The originals of the SAE forms (both initial and follow-up reports) are kept at the sites in the Investigator's file.

11.5 Reporting of individual SAEs and SUSARs by the sponsor

The SAKK CC ensures that all reporting requirements and timelines for reporting, as defined in the Swiss HRA and its applicable ordinances are followed.

The SAKK CC will forward any SAE which is fatal or resulted in death to the involved EC.

The SAKK CC will report every SUSAR to all principal investigators, to the involved ECs and to Swissmedic in accordance with the Swiss HRA.

Additionally, SAKK CC will forward each individual SAE and SUSAR to the coordinating investigator and to AstraZeneca.

11.6 Reporting of safety signals

In case the investigator receives external safety reports/letters related to the IMP, he/she must report to the sponsor within 7 days. The SAKK CC will forward these reports/letters to all investigators and to the local and lead ECs if applicable.

11.7 Pregnancy

Pregnancy itself or pregnancy of a patient's partner is not regarded as an AE unless there is suspicion that the trial IMP may have interfered with the effectiveness of a contraception medication. In the case of pregnancy occurring during the trial treatment or during 90 days after the last dose of MEDI4736, the investigator must report the event to the SAKK within 24 hours of knowledge of the event by completing the SAKK pregnancy reporting form. This form (available on the SAKK website (www.sakk.ch → Members → Trials → Lung Cancer → SAKK 16/14 → CRFs) has to be filled in immediately and faxed to the SAKK CC. The investigator shall ensure that the case is followed up until the end of the pregnancy and supply a final report on the outcome to the

SAKK CC. In addition, the investigator has to report any fetal anomaly, stillbirth, miscarriage or any other significant medicinal event concerning the pregnancy as SAE (see section 11.1.1).

Patients who become pregnant during trial treatment will be transferred to the follow-up phase of the trial (see section 9.7).

In case the female partner of a male patient becomes pregnant while the patient is on trial treatment or in the follow-up period of the trial, the patient should, with his partner's consent, notify the investigator. It is recommended that the investigator shall ensure that the case is followed up until the end of the pregnancy and supply a final report on the outcome to the SAKK CC.

The SAKK CC will forward within 1 working day each individual pregnancy report to the coordinating investigator and to AstraZeneca after receipt from the site. SAKK CC will endeavor to collect follow-up information and distribute final reports on pregnancy outcome to AstraZeneca in due time.

11.8 Periodic reporting on safety

The SAKK CC ensures that the reporting requirements and timelines for reporting, as defined in the respective applicable laws, are followed.

A development safety update report (DSUR) will be provided to the local investigators for filing into the investigator's file. The SAKK CC will submit the DSUR to the involved ECs, to Swissmedic and to AstraZeneca.

12 EVALUATIONS AND INVESTIGATIONS BEFORE, DURING AND AFTER TRIAL TREATMENT

Assessments and investigations must be done within the defined time as indicated below.

At the start of each therapy cycle (with chemotherapy or immunotherapy), assessments may be done one day before or on the day of therapy administration (d-1 or d1 of each cycle) unless otherwise specified in text below.

During the therapy cycle, weekly assessments may be done within ± 1 day of the indicated day.

A schedule of assessments and treatments is provided in Appendix 8. An adaptable scheduler (MS Excel file) can be downloaded from the SAKK website (www.sakk.ch → Members → Trials → Lung Cancer → SAKK 16/14).

12.1 Pretreatment evaluations and procedures

Informed consent must be obtained before registration and prior to any trial-specific procedures.

12.1.1 The following investigations have to be performed before registration:

- Histological confirmation of NSCLC
- Confirmation of the availability of tumor material (preferably histology, cytology allowed) at diagnosis for Central Pathology

12.1.2 The following investigations have to be performed within 42 days before registration

- Brain MRI or CT to exclude brain metastasis
- Pulmonary function tests according to ESTS guidelines, as depicted in Appendix 7 [75]
- Echocardiography to evaluate cardiac function

12.1.3 The following investigations have to be performed within 28 days before registration

- PET/CT with contrast enhanced CT scan of thorax and upper abdomen (incl. the assessment of number and size of lymph nodes)
- Tumor staging to confirm stage T1-3N2M0 (stage IIIA/N2) disease according to the process chart depicted in Appendix 6. One of the following investigations has to be performed:
  - Mediastinoscopy
  - Endobronchial ultrasound (EBUS) with FNA
  - Bronchoscopy with FNA
  - Esophageal ultrasound with FNA
- 12-lead ECG (in triplicate, 2-5 minutes apart)

12.1.4 The following investigations have to be performed within 14 days before registration

- Medical history, including baseline symptoms, concomitant corticosteroids, smoking habits, weight loss over 6 months, Charlson Comorbidity Index [82]
- Physical examination, including assessment of WHO performance status, weight, height and blood pressure
- Hematological values: hemoglobin, absolute neutrophils count, platelets count, WBC
- Hepatic function: bilirubin, AST/ALT, AP
- Metabolic function (serum or plasma): sodium (Na), potassium (K), magnesium (Mg)
- Renal function: serum creatinine and calculated creatinine clearance (according to the formula of Cockcroft-Gault, see Appendix 3)

- Thyroid function test: thyroid-stimulating hormone (TSH); free T3 and free T4 only if TSH abnormal
- Urine analysis*: bilirubin, blood, glucose, ketones, pH, protein, specific gravity, color and appearance (*microscopy should be used as appropriate to investigate white blood cells (WBC) and use the high power field for red blood cells)

Within 14 days prior to registration until d1 of treatment (but before the first dose of treatment)

- *Mandatory:* samples for translational research projects
    - 30 ml heparinized blood, 10 ml serum blood and 2.5 ml PAXgene blood (see section 18.4)
    - *Note*: histology or cytology samples for (retrospective) central review must be shipped to Central Pathology at the latest 30 days following registration (see section 17.1.3)
- *Optional: (only for patients who indicated their consent in main PIS/IC)*
    - Stool (see section 18.4)

Within 7 days prior to registration:

- Serum pregnancy test (for women of childbearing potential only)

12.2 Evaluations during neoadjuvant chemotherapy

Visits will take place weekly during the 3 cycles of neoadjuvant chemotherapy.

On day 1 of each cycle

d1, 22 and 43

- Physical examination including assessment of WHO performance status, weight and blood pressure
- Hepatic function: AST/ALT
- Renal function: creatinine and calculated creatinine clearance (according to the formula of Cockcroft-Gault, see Appendix 3)
- Metabolic function (serum or plasma): Na, K, Mg

On day 1 of each cycle and weekly thereafter

d1, 8, 15, 22, 29, 36, 43, 50 and 57

- Hematological values: hemoglobin, absolute neutrophils count, platelets count, WBC
- AEs

During cycle 3 of neoadjuvant chemotherapy

Between d50-d63 (corresponds to weeks 8-9)

- Radiological assessment with PET/CT with contrast enhanced CT scan of thorax and upper abdomen [83].

Note:

- Patients who permanently discontinue neoadjuvant chemotherapy due to AE and proceed to MEDI4736 therapy have to undergo a radiological re-assessment with PET/CT with contrast enhanced CT scan of thorax and upper abdomen within one week before starting MEDI4736.

Further investigations may be performed according to local standards.

12.3 Evaluations during neoadjuvant MEDI4736 therapy

Visits will take place weekly during the two cycles of neoadjuvant treatment with MEDI4736.

On day 1 of cycle 1

d64 (week 10)

- 12-lead ECG (in triplicate, 2-5 minutes apart) prior treatment administration
- Thyroid function test: TSH; free T3 and free T4 only if TSH abnormal
- Urine analysis*: bilirubin, blood, glucose, ketones, pH, protein, specific gravity, color and appearance (*microscopy should be used as appropriate to investigate WBC and use the high power field for red blood cells)
- *Mandatory:* samples for translational research projects
    - 30 ml heparinized blood, 10 ml serum blood and 2.5 ml PAXgene blood (see section 18.4)

On day 1 of each cycle

d64 (week 10) and d78 (week 12)

- Physical examination including assessment of WHO performance status and weight
- **Vital signs** (temperature, blood pressure, pulse rate, and respiratory rate) measured within one hour prior to start of MEDI4736 administration, at 30 minutes during the infusion (± 5 minutes), at the end of infusion (± 5 minutes), and at 30 minutes (± 5 minutes) post-infusion.
- After the first infusion (cycle 1, day 64) vital signs must also be measured 60 minutes (± 5 minutes) post-infusion.

On day 1 of cycle 1 and weekly thereafter

d64, 71, 78 and 85

- Hematological values: hemoglobin, absolute neutrophils count, platelets count, WBC
- Clinical chemistry (serum or plasma): creatinine, AST/ALT, Na, K, Mg
- AEs

Further investigations may be performed according to local standards.

12.4 Evaluations at surgery

Surgery must take place 2-4 weeks after the last infusion of MEDI4736.

The following assessments have to be done during the week preceding the surgery.

- Physical examination including assessment of WHO performance status, weight and blood pressure
- Hematological values: hemoglobin, absolute neutrophils count, platelets count, WBC
- Clinical chemistry (serum or plasma): creatinine, AST/ALT, Na, K, Mg
- Coagulation parameters: prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR)
- Thyroid function test: TSH; free T3 and free T4 only if TSH abnormal
- AEs
- 12-lead ECG (additional echocardiography at the local investigator's discretion)
- Pulmonary function tests (according to ESTS guidelines)
- PET/CT with contrast enhanced CT scan of thorax and upper abdomen (may be done up to 2 weeks preceding surgery)
- *Mandatory:* samples for translational research projects
    - 30 ml heparinized blood, 10 ml serum blood and 2.5 ml PAXgene blood (see section 18.4)

After surgery:

- AEs
- *Mandatory:* samples for central pathology review and translational research projects
    - Resected tumor specimen must be sent to Central Pathology (see section 17.1.3)

During radiation therapy:

For patients with R1/R2 resection (including patients with extracapsular spread of lymph node metastasis) undergoing radiotherapy, the investigator must collect and record the following assessments during the entire course of the radiation therapy:

- AEs

12.5 Evaluations during adjuvant MEDI4736 therapy

Adjuvant treatment with MEDI4736 should start within 4-6 weeks after surgery (or within 2 weeks after the completion of radiotherapy, when applicable) and will be administered for a maximum of 1 year (26 cycles).

Visits will take place on day 1 of each cycle.

On day 1 of each cycle

- Physical examination including assessment of WHO performance status and weight
- **Vital signs** (temperature, blood pressure, pulse rate, and respiratory rate) measured within one hour prior to start of MEDI4736 administration, at 30 minutes during the infusion (± 5 minutes), at the end of infusion (± 5 minutes), and at 30 minutes (± 5 minutes) post-infusion.
- AEs

On day 1 of cycle 1 and every other cycle thereafter

- Hematological values: hemoglobin, absolute neutrophils count, platelets count, WBC
- Clinical chemistry (serum or plasma): creatinine, AST/ALT, Na, K, Mg
- Thyroid function tests: TSH; free T3 and free T4 only if TSH abnormal
- Urine analysis*: bilirubin, blood, glucose, ketones, pH, protein, specific gravity, color and appearance (*microscopy should be used as appropriate to investigate WBC and use the high power field for red blood cells)

On day 1 of cycle 1 and cycle 9

- 12-lead ECG (in triplicate, 2-5 minutes apart) prior treatment administration

On day 1 of cycle 5

- *Mandatory:* samples for translational research projects
    - 30 ml heparinized blood, 10 ml serum blood and 2.5 ml PAXgene blood (see section 18.4)
- *Optional (only for patients who indicated their consent in main PIS/IC):*
    - Stool (see section 18.4; distribute the collection tube to the patient at cycle 4).

Every 3 months after the start of adjuvant treatment, starting 1 month after surgery

i.e. month 1, 4, 7, 10 (± 1 week) after surgery

- Contrast enhanced CT scan of thorax and upper abdomen

For all patients without previous disease progression/relapse: **a contrast enhanced CT scan of thorax and upper abdomen has to be performed at 12 months post-registration (+ 4 weeks), unless such a CT scan is already performed within the 6 weeks preceding the 12-month post-registration time-point during the regular schedule of assessment** (i.e. month 1, 4, 7, 10 after surgery). This tumor assessment is crucial for the evaluation of the primary endpoint (12 months EFS).

12.6 Evaluations at the end of treatment

Assessments are to be done within 1 month following the last dose of MEDI4736 in case of treatment completion as per protocol or after premature treatment termination (for any of the reason as mentioned in 9.7).

- 12-lead ECG (in triplicate, ≥2-5 minutes apart)
- Hematological values: hemoglobin, absolute neutrophils count, platelets count, WBC
- Clinical chemistry (serum or plasma): creatinine, AST/ALT, Na, K, Mg
- Thyroid function tests: TSH; free T3 and free T4 only if TSH abnormal
- X-ray
- AEs
- *Mandatory:* samples for translational research projects
    - 30 ml heparinized blood, 10 ml serum blood and 2.5 ml PAX blood (see section 18.4)

12.7 Evaluations at recurrence

At the time of tumor progression/relapse (only if it occurs during adjuvant trial treatment or within 30 days after the end of adjuvant treatment)

- *Mandatory:* samples for translational research projects
    - 30 ml heparinized blood and 10 ml serum blood (see section 18.4)
- *Optional:* (*requires additional patient informed consent)*
    - Tumor re-biopsy (preferred) or cytology (see section 17.1.3)

12.8 Evaluations in the follow-up phase

Patients will be followed-up lifelong. Follow-up visits will take place:

- every 3 months (± 2 weeks) during the first two years after the end of trial therapy,
- every 6 months (± 1 month) during the next three years until 5 years,
- yearly (± 1 month) until patient death (unless clinically indicated otherwise).

Patients without recurrence who are transferred to the follow-up phase before completion of trial treatment are followed as patients completing therapy without progression.

12.8.1 Patients without recurrence

- Physical examination
- Contrast enhanced thorax CT scan alternating with chest X-ray
  (every 3 months within 2 years after end of therapy; afterwards, every 6 months until 5 years after the end of therapy or until disease progression/relapse).

  Five years after the first follow-up visit, no further imaging is requested by the protocol.
- For all registered patients without previous disease recurrence: **a contrast enhanced CT scan of thorax and upper abdomen has to be performed at one year post-registration (+ 4 weeks), unless already performed within the 6 weeks preceding the 12-month post-registration time-point during the regular schedule of assessment as described above**.
  This assessment is crucial for the evaluation of the primary endpoint (12 months EFS).

Hematological and blood chemistry analyses may be done according to local standards.

12.8.2 Patients after recurrence

After the patient experienced progression, no trial-specific clinical assessments are requested. Further treatments and investigations are at the discretion of the treating physician.

- Survival status
- Reporting of subsequent therapies

13 CRITERIA OF EVALUATION AND DEFINITION OF ENDPOINTS

13.1 Criteria of evaluation

The following population sets will be used for the analysis:

- Full analysis set (FAS): is defined as all patients who received at least one dose of chemotherapy, excluding patients with major eligibility violations (as defined in the Statistical analysis Plan (SAP)).
- Full analysis set-2 (FAS-2): is defined as all patients who received at least one dose of chemotherapy and at least one dose of anti-PD-L1 antibody MEDI4736, excluding patients with major eligibility violations (as defined in the SAP).
- Per protocol (PP) set: is defined as a subset of patients of the FAS population excluding patients who did not receive full trial treatment (at least one dose of chemotherapy, followed by at least one dose of neoadjuvant MEDI4736, surgery and then at least one dose of adjuvant MEDI4736) or patients who had major protocol violations (as defined in the SAP).
- Safety set: is defined as all patients who took at least one dose of the trial treatment after registration.

In case of uncertainty, the coordinating investigator together with the trial team will decide, prior to the analysis and without looking at any efficacy data, if a patient can be included in the FAS, FAS-2 or PP set.

The patients who do not comply with the FAS criteria will not be taken into consideration for the efficacy endpoints.

13.2 Definition of Endpoints

13.2.1 Primary endpoint

EFS at 12 months

EFS at 12 months is defined as absence of events at 12 months after registration. EFS and event definition are given in section 13.2.2 below.

13.2.2 Secondary endpoints

EFS

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 (see Appendix 1).
- 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.

OS

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.

OR after neoadjuvant chemotherapy

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.

OR after neoadjuvant immunotherapy

OR after neoadjuvant immunotherapy is defined as complete response (CR) or partial response (PR) after the end of neoadjuvant immunotherapy. Response will be evaluated according to RECIST 1.1 criteria.

Patients without response assessment after the end of neoadjuvant immunotherapy will be regarded as having a non-evaluable response (NE) and shall be considered as failures for this endpoint.

pCR

pCR is defined as complete absence of any residual tumor in the primary tumor or in the involved lymph nodes or any suspicion of metastasis after the surgery of the patient.

Patients who were not operated will not be taken into consideration for this endpoint. Results from Central Pathology will be used.

Major pathological response (10% or less residual viable tumor [84]**)**

Major pathologic response is defined as the presence of 10% or less of the residual viable tumor after surgery.

Patients who were not operated will not be taken into consideration for this endpoint. Results from Central Pathology will be used.

Nodal down-staging to < ypN2

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.

Complete resection

Complete resection is defined as fulfillment of all the following criteria, according to [74]:

- free resection margins proved microscopically (R0 resection)
- mediastinal nodal dissection
- no extracapsular mediastinal nodal involvement
- no involvement of nodal resection margins (nodal stations 2 and 9)

Patients who were not operated will not be taken into consideration for this endpoint.

Pattern of recurrence (local, loco-regional, distant)

Pattern of recurrence is defined as location of first tumor progression or relapse. Patterns can be local (area of primary tumor or mediastinum), loco-regional or distant.

A separate category will include the combination of the above patterns.

Cases of patients with secondary malignancy or patients with no progression/relapse will not be taken into consideration for this endpoint.

AEs

All AEs (incl. abnormal vital signs) will be assessed according to NCI CTCAE v4.03 (see section 10.2).

Postoperative 30-day mortality

Postoperative 30-day mortality is defined as the case when a patient’s death occurs within 30 days from the thoracic surgery to remove the primary tumor.

Patients who were not operated will not be taken into consideration for this endpoint.

14 DOCUMENTATION

14.1 CRFs and reports

CRFs specifically created for this trial are used for documentation. It is very important to adhere to the schedule of visits prescribed in the protocol for all patients.

The eCRFs have to be completed online in the web-based EDC system (www.sakk.ch/edc) in a timely manner. The data should be entered into the eCRFs within a month from the patient's visit or medical examination.

Sites must use a patient identification list in order to allow identification of a patient. This list must be kept at the site in the investigator's file.

14.2 Notes for special handling of CRFs

Eligibility CRF:

- The completed form ER in the web-based EDC system has to be printed and signed by the treating investigator (authorized physician according to the staff list). **A copy of the signed form ER has to be sent to SAKK CC by email or fax within one month after the patient's registration.** The original signed form (or a copy thereof, in case the original was sent to SAKK CC), is kept at the site in the Investigator's file.
- If it is not possible to enter the eligibility form online for technical reasons, complete the paper CRF version and fax it in due time to the SAKK CC, which will perform the registration of the patient (see also section 7).

SAE and pregnancy report forms:

- Trial-specific SAE report forms and the pregnancy report forms have to be submitted **by fax** to SAKK CC **within 24 hours** of becoming aware of the SAE or pregnancy (see section 11 for SAE reporting and pregnancy reporting). Originals of SAE and pregnancy report forms are kept at the site in the Investigator's file.

AESI report forms:

- Non-serious AESIs are reported in the web-based EDC system on an AE form (the tick-box whether the event is an AESI must be checked).
- Serious AESIs are reported **within 24 hours** of becoming aware of the event using the trial-specific SAE report form mentioned above, **in case the AESI complies with the definition for seriousness.**

14.3 Source data

Additionally to other source data, the following data entered directly into trial documents are considered to be source data:

- patient screening and enrollment list,
- patient identification list,
- drug inventory log.

15 STATISTICAL CONSIDERATIONS

15.1 Introduction

The primary endpoint of this trial is EFS at 12 months after registration, with the intention to show promising efficacy results of the proposed therapeutic scheme compared to the standard of care.

In the standard of care, EFS at 12 months was 48% (primary analysis of trial SAKK 16/00) [35]. Final results of trial SAKK 16/96 were similar. An EFS rate at 12 months of at least 65% is required in order to consider the proposed therapeutic scheme as promising.

15.2 Sample size estimation

- Software package: R 3.2 (FixDes {OptInterim})
- Number of treatment arms: 1
- Type of design: Single stage design based on EFS rate at a specific time-point
- Null hypothesis: EFS at 12 months ≤ 48% [35]
- Alternative hypothesis: EFS at 12 months ≥ 65%
- Type I error: 0.05
- Power: 0.8
- Number of interim analyses for the primary endpoint: 0
- Expected accrual rate: 2 patients per month
- Expected proportion of non-evaluable patients: 5% (4 patients)
- Minimum sample size needed for the primary endpoint estimation: 64
- Total sample size: 68
- Expected accrual duration: 3 years
- Minimal follow-up time for primary analysis: 12 months from registration
- Expected trial duration until primary analysis (accrual duration + minimal follow up): 4 years

15.3 Interim safety analysis

An interim safety analysis may be performed after the first 25 included patients according to the following rule. The 30-day postoperative mortality rate will be calculated as soon as a period of 30 days after the patients' surgeries is completed. In case of a postoperative 30-day mortality >10%, a safety interim analysis will be performed and the independent data monitoring committee (IDMC) appointed by the SAKK Board will have to evaluate the safety of the trial and suggest appropriate measures (a detailed description of the interim data monitoring procedure will be specified in a dedicated IDMC charter). During the safety analysis, trial accrual will be suspended.

The SAKK Board will decide on trial continuation or premature termination based on the recommendations of the IDMC.

15.4 Statistical analyses

The primary analysis will take place only after all patients who comply with the FAS criteria have been followed at least for a period of 12 months after registration or until they experience an event, if this occurs first.

All efficacy endpoints will be analyzed using the FAS unless otherwise specified. Supportive analyses based on the FAS-2 and PP set will be performed. All safety endpoints will be analyzed using the safety set.

For the primary endpoint, the point estimate of EFS at 12 months together with its 90% confidence interval will be presented using the Kaplan-Meier estimators of the survival function.

Generally for each categorical variable the results will be summarized by frequencies and percentages. For each continuous variable the results will be summarized by descriptive statistics. All time-to-event endpoints shall have the median value estimated using the Kaplan-Meier method, along with a 95% confidence interval (CI). The number and type of events of each endpoint shall be presented descriptively by frequency and percentage.

Laboratory values will be expressed as absolute values and as grading (ordinal categorical variables) according to NCI CTCAE v4.03.

AEs will be presented by type and Grade in listing tables showing frequency and percentage of the within-patient worst grades. In addition, Grade ≥ 3 AEs and AEs with relation to treatment at least probable will be summarized separately.

No adjustment will be made for multiple testing.

Full analysis details will be outlined in the SAP.

15.5 Handling of missing data and drop-outs

No imputation of missing data will be performed.

A row denoted “Missing” will be included in count tabulations if necessary to account for drop-outs and missing values. As mentioned in section 13.1, patients not fulfilling the FAS criteria will not be taken into consideration for the efficacy endpoints.

16 QUALITY OF LIFE

Not applicable

17 PATHOLOGY

In order to uniformly assess the pathological response to neoadjuvant treatment (chemotherapy and immunotherapy), a central histopathological review will be performed. For that purpose, surgical specimens will be reviewed.

Histological diagnosis is highly recommended, however cytology specimens only are acceptable. Biopsy of the primary tumor is recommended. However, if biopsy of the primary tumor is technically or due to the expected complications not feasible, a radiologically highly suspicious lymph node may be used for resection or biopsy to obtain histological material.

17.1 Local pathology

17.1.1 Task for the local investigator

The local investigator at each participating site is responsible to inform the local surgeon and the local pathologist about the protocol, the trial-specific requirements and the sample handling for central pathological review and investigations and sample banking.

It is the task of the local investigator to determine the disease stage according to the TNM classification (7th edition, October 2009, Appendix 2) and to order the tumor material by the local pathologist (see 17.1.3).

17.1.2 Task for the local pathologist

The main task of the local pathologist is the diagnostic work-up of biopsy and resection specimens in a routine manner considering the following instructions:

Baseline biopsy or cytology at diagnosis (pre-treatment)

- The local pathologist must diagnose and subtype NSCLC by using as little tumor material as possible (we only recommend p40 and TTF1), so that enough can be sent to Central Pathology for review and translational studies.
- Diagnostic workup and NSCLC subtyping should be performed according to the WHO classification (4th edition, 2015) [85].
- Immunohistochemistry should only be performed if necessary and should be restricted to a minimum panel of markers.

Resection specimen after neoadjuvant treatment

- The local pathologist must examine the resection specimen in accordance with the protocol of the College of American Pathologists (which is available under the following link: http://www.cap.org/ShowProperty?nodePath=/UCMCon/Contribution%20Folders/WebContent/pdf/lung-13protocol-3300.pdf).
- The percentage of vital tumor tissue compared to the tumor bed should be evaluated macroscopically and microscopically and should be documented in the pathology report.
- In addition to the vital tumor, the whole tumor bed (fibrosis/necrosis) should be measured and at least one block per cm of the tumor bed should be embedded (not only the vital tumor areas). If no vital tumor is visible the whole tumor bed has to be examined histologically.
- Pathological TNM staging must be done according to the latest TNM classification (7th edition, October 2009 (see Appendix 2).

Biopsy or cytology at recurrence (post-surgery)

Only for patients who separately consented to the optional translational research *(if recurrence is within the time of adjuvant treatment or within 30 days after completion of adjuvant treatment)*

Re-biopsy is highly recommended, however cytology specimens only are acceptable.

- The local pathologist must confirm recurrence in a routine manner by using as little tissue as possible, so that enough tissue can be sent to Central Pathology for translational studies.
- Predictive marker analyses, if necessary, should be performed in a routine manner.

17.1.3 Required material for pathological review

The local investigator will order and ship the required following material to Central Pathology, together with the "Pathology sample cover letter" provided on the SAKK website (www.sakk.ch → Members section → Trials → Lung Cancer → SAKK 16/14 → trial tools):

Baseline biopsy or cytology at diagnosis (pre-treatment)

- if NSCLC is confirmed (preferably by histology) by the local pathologist, the local investigator will order the following material from the biopsy after registration of the patient:
  - max 5 cytology specimen containing tumor, preferably from the primary tumor (and the formalin-fixed and paraffin-embedded (FFPE) cell block, if available).
  - Or in case a histology sample is available: one hematoxylin and eosin (HE)-stained slide and the FFPE tumor tissue block or alternatively 10 unstained slides.
  - A copy of the local pathology report coded with the patient's UPN (*patient information such as name and date of birth must be erased*).

Resection specimens after neoadjuvant treatment

- The local investigator will inform the responsible surgeon that the patient is enrolled in the trial.
- The surgeon will send the resection specimen to the local pathologist in a routine manner with a note on the local pathology order form that the patient is enrolled in the trial (SAKK 16/14).
  - HE-stained histological slides from all tumor-containing blocks of the tumor and the tumor bed.
  - One representative FFPE block from the primary tumor site or the tumor bed in case of complete tumor regression and of one mediastinal lymph node metastasis if available, or alternatively 10 empty sections from representative FFPE blocks (blocks are preferred).
  - A copy of the local pathology report, coded with the patient's UPN (*patient information such as name and date of birth must be erased*).

Biopsy or cytology at recurrence (post-surgery)

Only for patients who separately consented to the optional translational research *(if recurrence is within the time of adjuvant treatment or 30 days thereafter)*

- The local investigator will inform the responsible pneumologist/radiologist that the patient is enrolled in the trial.
- The pneumologist/radiologist will take a biopsy (preferred) or cytology and send it to the local pathologist in a routine manner with a note on the local pathology order form that the patient is enrolled in the trial (SAKK 16/14).
  - 5 cytology specimen containing tumor (and the FFPE cell block, if available).
  - Or in case a histology sample is available: one HE-stained slide and the FFPE tumor tissue block or alternatively 10 unstained slides (blocks are preferred).
  - A copy of the local pathology report, coded with the patient's UPN (*patient information such as name and date of birth must be erased*).

Return of diagnostic samples: Any diagnostic sample can be returned to the site for diagnostic purposes and upon request from the local investigator or pathologist. Patients and their treating physicians have the right to be informed of the results of the central pathology review and investigations. Central Pathology will forward this information to any investigator whose patient or their treating oncologist expresses their wish to be informed.

Reimbursement for the local pathologist

The work of the local pathologist will be financially compensated by SAKK according to the SAKK guidelines on the pricing for Pathology (see "Principles of Translational Research in SAKK Trials").

Reconciliation listings

The local pathologist will be requested to provide at regular intervals a listing of all shipped samples to Central Pathology and SAKK CC for reconciliation. Timing for the reconciliation will be determined by the SAKK CC and communicated to the sites during trial conduct.

17.1.4 Labeling and handling

All material has to be clearly labeled with:
SAKK 16/14
Patient UPN
Date of sampling
Sample ID of local pathology institute
Site

17.1.5 Shipment

Samples, including the accompanying documents, have to be shipped within one month of registration/ patient surgery/ biopsy or cytology at recurrence (if applicable) with priority postal mail to:

Dr. med. Spasenija Savic
Trial SAKK 16/14
Institute of Pathology, USB
Schönbeinstrasse 40
CH – 4031 Basel

17.2 Central pathology

17.2.1 Task for the central pathologist

The central pathologist will review the shipped tumor material and lead the pathological investigation with the samples. Examinations will be performed in accordance with the WHO classification (4th edition, 2015) and the protocol of the College of American Pathologists.

The review data will be entered in the EDC system by the central pathologist.

Baseline biopsy or cytology at diagnosis (pre-treatment) and biopsy or cytology at recurrence (post-surgery) if available

- The NSCLC subtype will be confirmed (acc. to WHO classification, 4th edition, 2015) [85].
- The ratio of cancer versus non-cancer tissue will be assessed
- The feasibility for translational studies will be assessed

Resection specimen after neoadjuvant treatment

- The pathological response to neoadjuvant treatment (% of vital tumor) will be confirmed
- The ratio of cancer versus non-cancer tissue will be assessed
- The feasibility for translational studies will be assessed.

Reconciliation listings

The central pathologist will be requested to send at regular intervals (in general, twice yearly) a list of all received samples to SAKK CC for information and reconciliation. Timing for the reconciliation will be communicated to the pathologist during trial conduct.

17.3 Pathology samples banking

In case the patient consented to the storage of the tumor material in the trial-associated Biobank, the tumor samples will be kept at the Institute of Pathology, University Hospital Basel, for a maximum of 10 years after the publication of the primary analysis, for future research in connection with NSCLC and according to the trial-specific Biobank Regulation (see section 18.7 for further considerations and procedures with respect to sample banking). Any new research on these samples that is not planned in this protocol must first be approved by the SAKK board and by the relevant Ethics committee.

In case the patient did not consent to the biobanking of his/her tumor material, any leftover material will be returned to the site after the mandatory translational research part of the trial is performed.

Any diagnostic sample can be returned to the site in case of need for diagnostic purposes.

18 TRANSLATIONAL RESEARCH

Tumor samples from diagnostic biopsy or cytology and surgical resection as well as blood and stool samples obtained at defined time points during the conduct of the trial will allow an observational exploratory translational research.

Any research question not included in the protocol has to be formulated in written. The additional project has to consider the funding of the research and must be approved by the SAKK Board and be submitted to the relevant Ethics Committees and regulatory authorities for authorization.

18.1 Determination of a pre- and post-therapeutic *„Tumor Immune Profile“* (mandatory)

Patient participation in the translational projects described in this section is mandatory. Patient consent for translational research with their biological material and clinical data collected at baseline and during trial treatment, will be obtained prior to patient's inclusion into the trial (with the use of the main PIS/IC form, mandatory for trial participation).

18.1.1 Rationale

Recent studies established that the balance between cancer progression and regression is strongly influenced by complex interactions between the tumor and the microenvironment. It is known that in some cancers the infiltration of T cells into the tumor microenvironment correlates strongly with tumor regression and patient survival [86, 87]. This has also been substantiated in mouse models which clearly highlight the concept of cancer immuno-surveillance and cancer immuno-editing [88, 89]. However, in addition to T cells, there is also a highly heterogeneous population of other immune cells that infiltrate tumors and interact with tumor cells. These complex interactions between tumors and their microenvironment create the immune landscape, i.e. the so-called tumor immunome, which is thought to considerably contribute to tumor progression or regression. The tumor immunome has started to be investigated in more detail only very recently. There is for example growing evidence of a prognostic impact of tumor-infiltrating B cells and dendritic cells in NSCLC [90-92].

The PD-1:PD-L1/2 pathway is a major mechanism of immune escape. Blockade of the PD-1:PD-L1/2 pathway has recently been shown to exert remarkable therapeutic activity in patients with advanced NSCLC, melanoma, prostate, renal cell and colorectal cancer [93, 94]. It remains to be investigated whether PD-L1 expression on immune cells of the tumor microenvironment or on tumor cells is more relevant as predictive marker for anti-PD-L1 immunotherapies. Moreover, the definition of a "positive" PD-L1 expression is variable across studies and may impact on trial results. In a clinical trial with the anti-PD-1 antibody nivolumab 68 tumor specimens from 41 patients were analyzed [93]. The only independent marker for response to therapy was PD-L1 expression by ≥5% of the tumor cells. PD-L1 expression by tumor-infiltrating immune cells had no significant impact on objective clinical response rate, though there was a significant correlation with clinical benefit. The presence of tumor-infiltrating lymphocytes (TILs) did not correlate with objective response to therapy, while infiltration of B-cells correlated positively with the grade of immune infiltration and PD-1 expression by T-cells. The presence of TILs was associated with PD-L1 expression, reflecting an immune active microenvironment. Results from several trials indicate that the ratios of the different functional immune cell subsets may be of greater importance than their absolute numbers [94]. However, apart from the CD4:CD8-ratio, no subgroup analysis was performed. Another limiting factor of most of the trials is the small sample size (only 12 subjects with NSCLC of whom only 3 had squamous cell histology). Furthermore, since several lines of evidence indicate, that PD-L1 expression as well as immune cell infiltration vary widely within different tumor entities and stages [95-97], the heterogeneous composition of tumors in the study population makes it difficult to draw firm conclusions with regard to specific tumor entities.

18.1.2 Objectives

In this trial we aim to:

- compare the tumor immunome before (treatment-naive) and after neoadjuvant chemo- and immunotherapy.

- investigate efficacy outcome parameters (EFS, OR, OS) in relation to tissue expression of PD-L1.
- investigate biomarkers for anti-PD-L1 treatment and their relation to efficacy endpoints of interest (EFS, OS and OR after neoadjuvant immunotherapy) in NSCLC. Historical control samples from previous SAKK trials will be used.

18.1.3 TR projects

- *Immunohistochemistry*

  Tumor material from each patient before treatment and at the time of resection will be centrally collected in the Institute of Pathology at the University Hospital Basel. Immunohistochemistry (IHC) will be used to quantify protein levels of PD-1 and PD-L1. PD-L1 will be scored based on the previously published scoring method [98, 99]: IHC 0 = <1%, IHC 1 = ≥1% but <5%, IHC 2 = ≥5% but < 10, IHC 3 = ≥10%. IHC 2/3 will be considered as "PD-L1 positive". Tumor cells and immune cells will both be evaluated. In addition, we will calculate the H-score for tumor cells, i.e. intensity (0-3) x percentage of stained carcinoma cells = IHC-score 0-300. In addition to PD-L1 an IHC panel of lineage marker proteins will be used to quantify the different categories of associated immune cells. Furthermore, tissue samples will be evaluated for the percentage of stromal TILs as recently recommended by an international working group [100]. Based on recent reports on the predictive role of CD8 expression at the invasive tumor margin [101], immunohistochemical analyses will specifically focus on the invasive tumor margin.

- *High-throughput mRNA sequencing and next-generation sequencing*

  We plan to perform a global gene expression profile of immune cells within tumor material at the time of diagnosis and at the time of surgical resection by using high-throughput mRNA sequencing. This analysis will include clonality assessment of the T cell receptor (T cell repertoire), neo-antigens and neo-epitopes as well as the tumor microenvironment. In particular, the latter will allow to obtain a global genetic profile of the tumor immune landscape to dissect the highly complex and diverse network of cancer infiltrating immune cell subsets.

  Next-generation sequencing (NGS) of genomic tumor DNA will be used to evaluate a panel of genes that are commonly mutated in NSCLC. NGS allows identification of driver mutations and of inactivation of tumor suppressor genes. Mutational analysis will be correlated to the tumor immunome.

- *Multiparameter flow cytometry of immune cell populations*

  Multiparameter flow cytometry of peripheral blood will allow us to obtain a view of the cellular landscape in the peripheral blood of NSCLC patients. Frequency and phenotype of lymphocyte subpopulations in the peripheral blood before, during and after neoadjuvant therapy will be investigated. The following cell types will be investigated using standard staining panels: T cells (including T follicular helper cells, effector T cells, regulatory T cells), B cells (including memory B cells, regulatory B cells), natural killer-(T) cells, myeloid cells (including TAMs and MDSCs). Furthermore, the expression of potentially inhibitory receptors on T cells will be assessed using commercially available antibodies including anti-CTLA-4, -PD-1, -BTLA, -CD160, -Tim-3, -2B4, -LAG3, -CD200R, -LilrB2, -NKG2A, -KIRs, -Siglecs and -CD57, which are considered key players in regulating T cell activation/inhibition [102]. We will further analyze the expression of these molecules on T cell subpopulations with respect to their activation status (e.g. CD25, CD69, CD137, ICOS, KLRG-1, OX40), their differentiation stage (e.g. CD45RA, CCR7, CD27, CD28, CD57, FoxP3), and their functional capacity (e.g. Ki-67, perforin, Granzyme B). In particular, the analysis will determine the expression pattern of those receptors on different T cell subsets, ranging from naïve to memory/effector status.

  Induction of cytotoxicity will be determined by measuring degranulation (CD107a) and Granzyme B expression. Secretion of effector cytokines such as IFN-γ, TNF-α, TGF-β, IL-2, IL-10 and IL-35 which are gradually lost during T cell exhaustion, will be measured by intracellular cytokine staining and ELISA assays. In order to compare T cell activation and function on naïve and memory subsets, markers for CD45RA and CCR7 will be included in all stainings.

- *Multiplexed cytokine detection with magnetic immunoassays (Serum)*

  We will use the Luminex MagPix system to quantitatively measure the changes of different cytokines in the peripheral blood of NSCLC patients following treatment. We will measure the amounts of 32 different cytokines known to play roles in innate and adaptive immunity.

18.2 Re-biopsies/cytologies in patients with tumor progression or relapse during adjuvant MEDI4736 treatment (*optional*)

In a separate *optional* research project, patients experiencing tumor progression or relapse **during adjuvant MEDI4736 therapy or within 30 days after the last dose of adjuvant MEDI4736 therapy** will be offered to undergo a re-biopsy or cytology of the tumor. Participation in this research project is non-mandatory and will be individually discussed with each patient. Patient consent will be obtained with the use of a separate patient informed information and consent form.

18.2.1 Objective

In order to better understand potential mechanisms associated with resistance towards checkpoint inhibition, we aim at investigating the immunome (by high-throughput sequencing and multi-parameter flow cytometry as described in section 18.1.3 above) as well as genomic aberrations in the tumor using NGS at the time of tumor progression.

18.3 Microbiome (*optional*)

Participation in this research project is *optional*. Patients will be informed prior trial entry and written patient consent will be obtained using the main patient information sheet and consent form.

18.3.1 Rationale

Recent data illustrate the complex interplay of microbial activity and function with the immune system. It was demonstrated that gut bacteria bolster the effects of chemotherapy as well as immunotherapy in mice [64, 65]. More recently, the influence of gut microbiota on the effect of immune checkpoint inhibitors has been demonstrated in an animal model [66]. Another study confirms the influence of gut microbiota on the activity of anti-CTLA-4 therapy also in melanoma patients [67]. This study showed that ipilimumab modifies the abundance of immunogenic Bacteroides species in the gut of melanoma patients, which in turn impacts its anticancer efficacy. Moreover, it has been shown that therapy with immune checkpoint inhibitors lead to the development of antibodies to components of the enteric flora [103].

18.3.2 Objectives

We aim at confirming the hypothesis that the gut microbiota is required for the anticancer effects of PD-L1 blockade. For this purpose we will collect stool samples from patients to analyze the gut microbiota composition by high throughput sequencing of feces in therapy-naïve patients and during therapy with MEDI4736. We aim at validating the relevance of the gut microbiota composition for efficacy of immune checkpoint inhibitors. Furthermore, we aim at understanding how immune checkpoint inhibition changes the host microbiome and how these changes correlate with the response of the disease to therapy.

18.4 Samples and scheduling of sampling

Except for PAXgene Blood RNA collection tubes and OMNIgene•GUT stool collection kits, no tube or shipping material will be provided by the SAKK CC. Sites have to use their own disposables.

Refer to the corresponding “TR useful tool” on the SAKK website for further information.

Mandatory samples

- **Diagnostic tumor samples** (histological or cytological) and **tumor resection specimens** which were sent to Central Pathology for the assessment of the pathological response to neoadjuvant treatment will be used for research projects.

  See sections 17.1.4 and 17.1.5 for the handling, labeling and shipment of tumor samples.

- **Peripheral blood** (30 ml, heparinized), **serum** (10 ml, native blood) and **preserved blood** (2.5 ml, PAXgene) will be collected by venipuncture during trial conduct:
  - At baseline (prior to the start of neoadjuvant chemotherapy)
  - Prior to the start of neoadjuvant MEDI4736 therapy
  - Prior to surgery
  - Prior to the 5th application of adjuvant MEDI4736 therapy
  - At the end of trial treatment (also in case of premature trial treatment end for other reasons than PD/relapse), or
  - At the time of tumor progression or relapse (if within the time of adjuvant MEDI4736 treatment or within 30 days thereafter)

  See also section 12.

Optional samples

- **Tumor biopsy** at the time of tumor progression/relapse or metastasis if within the time of adjuvant treatment or 30 days thereafter *(**requires additional patient informed consent**)*.
- **Stool** from patients who consented to the optional translational project *(**requires specific consent in main PIS/IC**)*
  - at baseline (prior to the start of neoadjuvant chemotherapy)
  - Prior to the 5th application of adjuvant MEDI4736 therapy

    Note: Be reminded to distribute the stool collection tube to the patient at cycle 4 of adjuvant immunotherapy.
    In addition, the patient is to be instructed that the stool should be collected towards the end of the 2-weeks cycle and that he/she should bring back the tube at the next visit (e.g. cycle 5).

Remaining samples of blood and tumor tissue material may be stored in a biobank after completion of the planned research projects (see 18.7). Any stool material left after completion of the planned investigation will be discarded.

18.5 Handling and labeling

Blood and stool samples have to be clearly labeled with:

SAKK 16/14
Patient UPN
Site
Sampling date

Blood samples have to be sent immediately upon collection. However, they should not be sent on Friday or during the weekend. In such cases, the blood can be kept at 4°C until shipment on Monday. Otherwise the samples can be stored and shipped at room temperature.

Stool should be shipped within one week upon return of the sample by the patient (as stool is stable in the collection tube for 2 weeks, ensure that the sample will reach the laboratory no later than 2 weeks after it is collected).

18.6 Shipment

Samples have to be sent to: Laboratory of Cancer Immunology
Sacha Rothschild / Franziska Uhlenbrock
Trial SAKK 16/14
Department of Biomedicine
Hebelstrasse 20 / Labor 416
CH – 4031 Basel

Shipment modalities are described in the corresponding “TR useful tool” which is posted on www.sakk.ch → Members → Trials → Lung Cancer → SAKK 16/14 → trial tools).

18.7 Sample biobanking

In case the patient consented to the storage of his/her biological material in the trial-associated Biobank, PBMCs (isolated from heparinized blood using FICOLL), serum samples and the PAXgene-preserved blood will be stored in the Laboratory for Cancer Immunology, Department of Biomedicine, University Hospital Basel according to the trial-specific Biobank Regulation, for future research in connection with NSCLC. Samples will be stored until publication of the primary analysis and up to 10 years thereafter.

In case the patient did not consent to the biobanking of his/her blood samples, any leftover material will be destroyed after the mandatory translational research part of the trial is performed.

The tumor material from consenting patients will be kept at the Institute of Pathology, University Hospital Basel, until publication of the primary analysis and up to 10 years thereafter, for future research in connection with NSCLC and according to the corresponding Biobank Regulation (see also section 17.3).

The banking of material must conform to the HRA and its corresponding ordinance HFV/ORH, and to the recommendations from the Swiss Ethics Committees on research involving humans. It is regulated by specific Biobank Regulations. The patient will have no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the samples.

The patient retains the right to have their stored material irreversibly anonymized at any time by contacting the principal investigator. The SAKK will be responsible for the anonymization of the sample(s) at the request of the patient. However, data which is already obtained from this material can be used for the intended analysis.

The SAKK will be responsible for the destruction of the sample(s) at the end of the storage period. The investigator will provide the sponsor with the required trial code and patient identification (UPN) so that any remaining sample can be located and destroyed.

Any new research on these samples that is not planned in this protocol must first be approved by the SAKK board and by the relevant Ethics committee.

19 ECONOMIC EVALUATION

Not applicable

20 ETHICAL CONSIDERATIONS

This protocol was written and the trial will be carried out in accordance with the principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by ICH, the applicable Swiss HRA and its associated ordinances and the requirements from the Swiss regulatory bodies [106].

The protocol, the patient information sheets and informed consent forms (PIS/ICs), as well as all other trial-related documents shall be submitted to all involved ECs and to the competent authority in agreement with local legal requirements for formal authorization. Any amendment to the protocol, the CRFs or the PIS/ICs will be submitted for authorization to these institutions.

The decision of the ECs and competent authority with regard to the conduct of the trial will be made in written to the Sponsor prior to trial initiation. Any substantial amendment to the protocol (except for safety reasons) can only be implemented at a site after obtaining written authorization by the regulatory bodies. Patient recruitment can only take place after the site has officially been opened for accrual by the SAKK CC.

Sites have to adhere to the Swiss HRA and all applicable local regulatory guidelines.

20.1 Risks/benefits

NSCLC stage IIIA(N2) is a potentially curable disease with poor cure rates still. In this trial we investigate the addition of the immune checkpoint inhibitor MEDI4736 to standard therapy. Therefore, all patients receive the standard of care which consists in three cycles of neoadjuvant chemotherapy with cisplatin/docetaxel followed by surgical resection of the tumor. We know from previous trials that immune checkpoint inhibition with anti-PD-L1 antibodies is an active treatment leading to tumor responses and long lasting tumor stabilization in metastatic disease. Therefore, there is a strong rationale to use these agents also in the curative setting to improve the outcome of the disease.

Patients will be exposed to the risk of additional occurrence of toxicities which are associated with the investigational product. Yet, the rate of grade 3 and 4 toxicities with MEDI4736 is below 5% and investigation product has shown so far a relatively safe profile.

The neoadjuvant use of MEDI4736 delays surgery, with the consequence that it holds the risk of tumor progression before surgery in patients not responding to the treatment. However, it is known from past trials that patients progressing within six weeks after platinum-based induction chemotherapy have an adverse prognosis. The benefit of an earlier surgical tumor resection in this patient subgroup is questionable. Our trial will closely monitor disease status during neoadjuvant treatment to offer the best-of-care off-trial therapy to patients who will progress before surgery.

To address this risk further, as this trial is the first one to investigate the neoadjuvant use of immune checkpoint inhibition in potentially curable NSCLC patients, we implemented an interim safety analysis. This analysis will be performed after the first 25 included patients. The 30-day postoperative mortality rate will be calculated as soon as a period of 30 days after the patient surgeries is completed. In case of a postoperative 30-day mortality >10%, an IDMC will have to evaluate the safety and suggest appropriate measures.

20.2 Trial categorization

Clinical trial with IMP.

MEDI4736 is an investigational product without marketing authorization for any indication. MEDI4736 is currently under investigation in 30 ongoing clinical trials either as monotherapy or as combination therapy for advance stage solid tumors. According to the Swiss HRA and its corresponding ordinance KlinV/Oclin on clinical trials, this trial is classified as category C.

20.3 Patient information and informed consent

The informed consent procedure must conform to the ICH-GCP guidelines.

All patients will be informed of the aims and procedures of the trial, the possible AEs, how to react in case an AE occurs, and possible hazards to which they will be exposed. They will be informed as to the strict confidentiality of their patient data and biological material, but they need to know that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician.

The investigator must provide the patient with sufficient opportunity to consider whether or not to participate and minimize the possibility of coercion or undue influence. The information provided shall be in a language intelligible to the patient and may not include any content that appears to waive any of the patient's legal rights, or appears to release the investigator, the sponsor, or the institution from liability for negligence.

It will be emphasized that participation is voluntary and that the patient is allowed to refuse further participation in the trial whenever he/she wants. This will not prejudice the patient's subsequent care.

Informed consent will be obtained before registration and prior to any protocol-specific procedures.

Informed consent shall be obtained on a written form approved by the local EC and signed and personally dated by the patient and the investigator. The patient information sheet as well as a copy or original of the signed and dated informed consent will be handed to the patient. Inclusion of legally incompetent patients is not permitted in this trial.

In case new results become available that shift the risk/benefit ratio, the patient should re-consent.

In this trial, the collection of tumor material and blood sampling for translational research purposes is mandatory. The patient will be made aware of the mandatory translational aspects of the trial. Patients refusing to accept mandatory translational research projects (and the associated collection of their biological samples) cannot participate in the trial.

Participation to the translational research project with stool is optional. Patient's consent for the optional collection of stool will be sought when the patient is informed about the trial (using the main PIS/IC). Patient's refusal will have no consequence on their participation in the trial.

Patient's consent to the banking of his/her blood and tumor material for future research projects and to the additional collection and banking of tumor sample at recurrence is optional and will not impact on the patient's participation in the trial. Separate information and consent forms will be presented to the patients for this purpose.

20.4 Premature withdrawal

Patients have the right to refuse further treatment for any reason and at any time. In that case, they will be transferred to the follow-up phase. Patients who decide to withdraw from the trial (i.e. refuse further data collection) will be informed that all data and biological material collected until the time point of their withdrawal will be used. For the patient's security, a last examination should be performed.

Patients may be withdrawn at any time from trial treatment at the discretion of the treating investigator due to an SAE or based on any other relevant medical condition. The patient will then be transferred to the follow-up phase.

21 ADMINISTRATIVE CONSIDERATIONS

21.1 Insurance

The SAKK will indemnify patients for damages they have suffered as participants in the trial. For this purpose, SAKK has taken out a special insurance for clinical trials with Chubb Insurance Company of Europe SE, Zollikerstrasse 141, 8034 Zürich.

21.2 Financing and support

This trial is funded by SAKK and the pharmaceutical company AstraZeneca. The study medicinal product MEDI4736 (durvalumab) is provided by AstraZeneca.

21.3 Monitoring and auditing

All source data must be accessible for auditing and monitoring. CRAs and auditors will maintain patient confidentiality.

21.3.1 Monitoring strategy

This trial will be monitored. The SAKK is following a risk-adapted monitoring strategy according to the concept developed by the ADAMON group [110] and the TransCelerate position paper . Based on the risk analysis, level 4 monitoring strategy has been chosen. The different monitoring activities as well as the frequency of the visit are described in a trial-specific monitoring plan.

21.3.2 Auditing/inspecting

Authorities have the right to perform inspections, and the SAKK has the right to perform on-site auditing during working hours upon reasonable prior notice.

21.4 IDMC

An IDMC appointed by the SAKK Board may evaluate the safety of the trial and suggest appropriate measures if necessary (see section 15). A detailed description of the interim data monitoring procedure will be specified in a dedicated IDMC charter.

21.5 Quality control and quality assurance

Several procedures ensure the quality of the trial in compliance with applicable regulatory requirements, GCP and the protocol:

- Written standard operating procedures are implemented
- Personnel involved in conducting the trial is qualified by education, training and experience
- An updated staff list must be kept at the site
- Validation of database and statistical analysis
- Quality control principles are implemented
- On-site and central monitoring to evaluate protocol compliance (SDV, verification of informed consent etc.) by personnel designated by the SAKK
- Data captured online will be validated in real-time, yielding errors (for inacceptable data) and warnings (for possibly inconsistent data - these warnings may be overruled by the user).
- Audit trail of changes
- Medical data review by the coordinating investigator or a delegated person (all CRFs will be reviewed and checked on medical content)
- Central management of deviations and implementation of corrective and preventive measures
- Central pathology review
- IDMC
- Safety monitoring

- Accountability of MEDI4736
- Internal audit procedures

21.6 Trial activation procedure

The procedure for trial activation at a site is described in the final protocol letter, which is sent to all sites which committed to participate in the trial. All participating sites must follow the instructions which are given in this letter for the preparation of site documents. Upon receipt of the sites documents, the SAKK CC will submit them to the involved ECs and Swissmedic.

Any site which is interested to participate in the trial, but has not committed yet, has to contact the SAKK CC first.

The investigator will only be allowed to register patients into the trial after the ECs and Swissmedic authorized the trial at the site and the SAKK CC opened the site for accrual.

21.7 Local trial records

21.7.1 Investigator's file

All trial-related correspondence should be filed in the investigator's file. A suggested table of contents (according to ICH E6, chapter 8) is provided on the SAKK website (www.sakk.ch → Members → Trials → Lung Cancer → SAKK 16/14 → trial tools).

21.7.2 Useful tools

CRFs, drug order forms and accountability logs, documents required for EC approval, the excel schedule of assessments, and any other trial tool can be downloaded from the SAKK website (www.sakk.ch → Members → Trials → Lung Cancer → SAKK 16/14 → trial tools).

21.7.3 Record retention

The site will retain all essential documents according to ICH-GCP. This includes copies of the patient trial records, which are considered as source data, patient informed consent statement, laboratory printouts, drug inventory and destruction logs, and all other information collected during the trial. These documents were stored until at least 15 years after the termination of the trial. The end of this retention period will be communicated to the sites by the SAKK CC**.** For the patient trial records, which are entered into the EDC system, the sponsor guarantees the access and availability of the data at any time for at least 15 years after the termination of the trial.

In the event that the principal investigator retires or changes employment, custody of the records may be transferred to another competent person who will accept responsibility for those records. Written notice of such transfer will be given to the SAKK CC. The SAKK will notify the concerned regulatory authorities.

21.8 Trial registration

The SAKK will register the trial at www.clinicaltrials.gov and on the Swiss National Clinical Trials Portal (SNCTP) at www.kofam.ch/www.humanforschunginfo.ch.

21.9 List of participating sites

A list of sites and investigators that have agreed to participate in the trial are given in a separate document which can be downloaded from www.sakk.ch (→ Members → Trials → Lung Cancer → SAKK 16/14 → trial tools).

21.10 Modifications of the protocol

21.10.1 Substantial amendment

Any amendment which may have an impact on the conduct of the trial, the potential benefit of the trial, or may affect patient safety, including changes of trial objectives, trial design, patient

population, sample sizes, trial procedures, or significant administrative aspects. Such an amendment must be accepted by the SAKK Board and must have the authorization of the respective EC and competent authority (if applicable) prior to implementation.

21.10.2 Safety amendment

A safety amendment is a special kind of substantial amendment which is released when it is necessary to eliminate immediate hazards to trial participants. A safety amendment requires immediate implementation at local sites and is submitted in parallel for authorization to the ECs and the competent authority (if applicable).

21.10.3 Non substantial amendment

Non-substantial amendments such as minor corrections and/or clarifications that have no effect on the way the trial is conducted have to be submitted to the ECs once a year, together with the submission of the annual development safety update report. Non-substantial amendments which affect the evaluation of the competent authority have to be submitted to the authority as soon as possible.

21.11 Trial termination

The SAKK CC is responsible for submitting the information about trial termination to the Swiss authorities according to the Swiss HRA.

22 PUBLICATION

The results of the trial will be published according to the current version of the SAKK publication guidelines (available on the SAKK website). The SAKK publication guideline guarantees the freedom of reporting of the participating physicians.

23 CONFIDENTIALITY

23.1 Copyright

The information contained in this protocol is copyright protected by the SAKK (Swiss Group for Clinical Cancer Research). This information is given for the needs of the trial and must not be disclosed to persons outside of the SAKK without prior written consent of the SAKK CC.

23.2 Confidentiality

Trial-related data of the patient will be provided in a coded manner to the SAKK CC. The names of the patients will not be disclosed to the SAKK CC. A unique patient number (UPN) will be attributed to each patient registered into the trial.

Identification of patients must be guaranteed at the site. For this purpose, sites are requested to use the patient screening and enrollment and the patient identification lists specifically produced for the trial. In order to avoid identification errors, the year of birth and the UPN have to be provided on the CRFs. Patient confidentiality will be maintained according to the applicable legislation. Patients must be informed of, and agree to, data and material transfer and handling, in accordance with Swiss data protection law.

All information concerning the IMP supplied by AstraZeneca in connection with this trial and not previously published is considered confidential and proprietary information.

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APPENDICES

Appendix 1 Tumor response assessment according to RECIST 1.1

All patients will be evaluated for response according to the revised Response Evaluation Criteria in Solid Tumors (RECIST v1.1) [112].

App 1.1 Methods of assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

- **CT** is the best currently available and reproducible method to measure lesions selected for response assessment. CT should generally be performed using a ≤ 5 mm contiguous reconstruction algorithm. **MRI** is acceptable for certain situations.
- **Clinical lesions** will only be considered measurable when they are superficial (e.g. skin nodules) and ≥ 10 mm. In the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended.
- Lesions on **chest X-ray** are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- **Ultrasound** is not useful in assessment of lesion size and should not be used as method of assessment.
- **FDG-PET** is generally not foreseen for regular response assessments. It may, however, be used to detect or confirm the appearance of new lesions. Attenuation correction CT scans performed as part of a **PET/CT** scan frequently show lower resolution; therefore, dedicated CT scans are preferred. However, if the site can demonstrate that the CT performed as part of a PET/CT is of the same diagnostic quality as a diagnostic CT (with i.v. and oral contrast), then the CT portion of the PET/CT can be used for RECIST measurements.

App 1.2 Definition of measurability

Measurable disease is defined as the presence of at least one measurable lesion.

- **Measurable lesions:**
  - **Non-nodal lesions** that can be accurately measured in at least one dimension with longest diameter ≥ 10 mm using CT scan, assuming the slice thickness is ≤ 5 mm. As a general rule, the longest diameter must be at least twice the slice thickness of the imaging. In the case of chest X-ray, the lesion must be ≥ 20 mm. Clinically assessed lesions must be ≥ 10 mm.
  - **Lymph nodes** that can be accurately measured with a short axis of ≥ 15 mm using CT scan, assuming the slice thickness is ≤ 5 mm.
- **Non-measurable lesions:** all other lesions, i.e. :
  - small non-nodal lesions (longest diameter < 10 mm in CT scan)
  - small lymph nodes (short axis ≥ 10 and < 15 mm) [1]
  - bone lesions[2]
  - leptomeningeal disease
  - ascites
  - pleural/pericardial effusion
  - inflammatory breast disease
  - lymphangitis cutis/pulmonis
  - cystic lesions[3]
  - tumor lesions situated in a previously irradiated area, or subjected to other locoregional therapy[4]

- abdominal masses/abdominal organomegaly identified by physical exam that are not measurable by reproducible imaging techniques

[1] Lymph nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed

[2] Lytic bone lesions or mixed lytic-blastic lesions, with *identifiable soft tissue components,* can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

[3] Cystic lesions thought to represent cystic metastases may be considered as measurable lesions. However, if non-cystic lesions are present, these are preferred as target lesions.

[4] May be considered measurable if there has been demonstrated progression in the lesion.

App 1.3 Selection of lesions

Selection of target lesions

Measurable lesions up to a maximum of 5 lesions representative of all involved organs, and up to 2 per organ, should be identified as target lesions and measured and recorded at baseline.

Target lesions (TL) should be selected on the basis of their size and their suitability for accurate repetitive measurements. A sum of diameters for all target lesions will be calculated and reported as the baseline sum of diameters. **Lymph nodes** selected as TL should always have the **short** axis recorded. **All other lesions** should always have their **longest** diameters recorded. This sum will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

Selection of non-target lesions

All other lesions (or sites of disease) should be identified as non-target lesions (NTL) and should also be recorded at baseline. Measurements are not required, but the presence or absence of each should be noted throughout follow-up. It is possible to record multiple NTL as a single item on the CRF (e.g. "multiple liver metastases").

App 1.4 Evaluation of lesions

Evaluation of Target Lesions

All TL will be measured at each tumor assessment, and the sum of their diameters will be compared to previous assessments in order to assign the response status as specified below.

- Complete Response (CR): Disappearance of all TL. Lymph nodes selected as TL must each have reduction in the short axis to < 10 mm in order for the response to be considered complete.
- Partial Response (PR): At least a 30% decrease in the sum of diameters of TL taking as reference the baseline sum of diameters.
- Progression (PD): At least a 20% increase in the sum of diameters of TL, taking as reference the smallest sum recorded on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Note: All TL, including lymph nodes, should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). If the radiologist does not feel comfortable assigning an exact measure and reports a lesion as "too small to measure", a default value of 5 mm should be recorded. If a TL is thought likely to have disappeared, "0 mm" is noted.

Evaluation of Non-Target Lesions

- Complete Response (CR): Disappearance of all NTL; lymph nodes selected as NTL must be non-pathological in size (< 10 mm).
- Non-CR/non-PD: Persistence of one or more NTL (non-CR).

- Progression (PD): unequivocal progression of existing NTL. *Unequivocal* means: comparable in magnitude to the increase that would be required to declare PD for measurable disease or an overall substantial increase in tumor burden that merits treatment discontinuation.

Determination of new lesions

The appearance of any new malignant lesions denotes disease progression. The finding of a new lesion should be unequivocal, i.e. not attributable to differences in scanning technique or findings thought to represent something other than tumor. If a new lesion is equivocal, e.g. because of its small size, the patient will stay on treatment (if the decision on PD is based on this lesion only). If the repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the previous scan.

Lesions found in a new location not included in the baseline scan (e.g. brain metastases) are considered new lesions.

Note: the "re-appearance" of a previously "disappeared" target or non-target lesion does not in itself necessarily qualify as PD; this is the case only if the overall evaluation meets the PD criteria, or if the patient was previously in CR.

Additional considerations

- In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.
- The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

App 1.5 Determination of overall response

Based on the responses of TL, NTL, and the presence or absence of new lesions, the overall response will be determined at each tumor assessment, according to the table below:

Target Lesions	Non-Target Lesions	New Lesions	Overall
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated (NE)*	No	PR
PR	Non-PD or not all evaluated*	No	PR
SD	Non-PD or not all evaluated*	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

* In selected circumstances, certain non-target organs may be evaluated less frequently. For instance, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

Note: a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression, sometimes reported as “symptomatic deterioration”, is not a response outcome in itself. Every effort should be made to document objective progression even after discontinuation of treatment.

Appendix 2 TNM Classification

According to UICC 2009 [112]

Primary tumor (T)	
TX	Primary tumor cannot be assessed, or the tumor is proven by the presence of malignant cells in sputum or bronchial washing but is not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor ≤ 3 cm in greatest dimension, surrounded by lung or visceral pleura, no bronchoscopic evidence of invasion more proximal than the lobar bronchus (not in the main bronchus); superficial spreading of tumor in the central airways (confined to the bronchial wall)
T1a	Tumor ≤ 2 cm in the greatest dimension
T1b	Tumor > 2 cm but ≤ 3 cm in the greatest dimension
T2	Tumor > 3 cm but ≤ 7 cm or tumor with any of the following: • Invades visceral pleura • Involves the main bronchus ≥ 2 cm distal to the carina • Associated with atelectasis/obstructive pneumonitis extending to hilar region but not involving the entire lung
T2a	Tumor > 3 cm but ≤ 5 cm in the greatest dimension
T2b	Tumor > 5 cm but ≤ 7 cm in the greatest dimension
T3	Tumor > 7 cm or one that directly invades any of the following: • Chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, or parietal pericardium; Or tumor in the main bronchus < 2 cm distal to the carina but without involvement of the carina Or associated atelectasis/obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe
T4	Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or carina; or separate tumor nodule(s) in a different ipsilateral lobe
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in the ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in the contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph nodes
Distant metastasis (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural (or pericardial) effusion
M1b	Distant metastasis

- **c**: stage given by clinical examination of a patient. The c-prefix is implicit in absence of the p-prefix.
- **p**: stage given by pathologic examination of the surgical specimen.
- **y**: stage assessed after neoadjuvant therapy.

Appendix 3 Calculation of creatinine clearance

Creatinine clearance should be calculated according to the formula of Cockcroft-Gault [113].
Cockcroft-Gault formula:

$$\text{Creatinine clearance (ml/min)} = \frac{(140 - \text{age}) \times \text{weight (in kg)} \times \text{constant}}{\text{serum creatinine (in µmol/L)}}$$

Constant is 1.04 for females and 1.23 for males

Appendix 4 WHO performance status

Performance status should be calculated according to the ECOG/WHO definition [114].

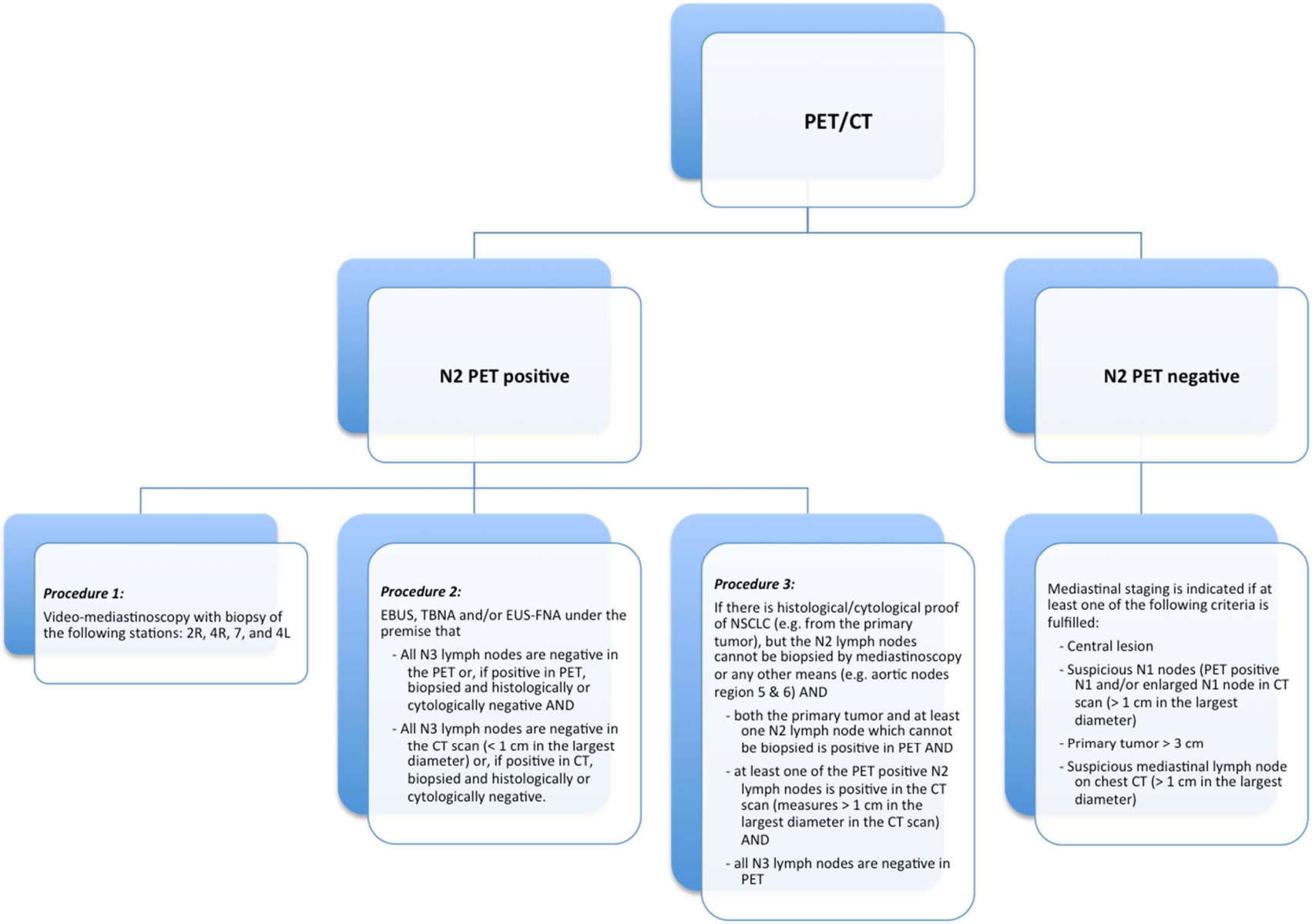
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out 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. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Appendix 5 New York Heart Association (NYHA) classification

From the Criteria Committee of the New York Heart Association [115].

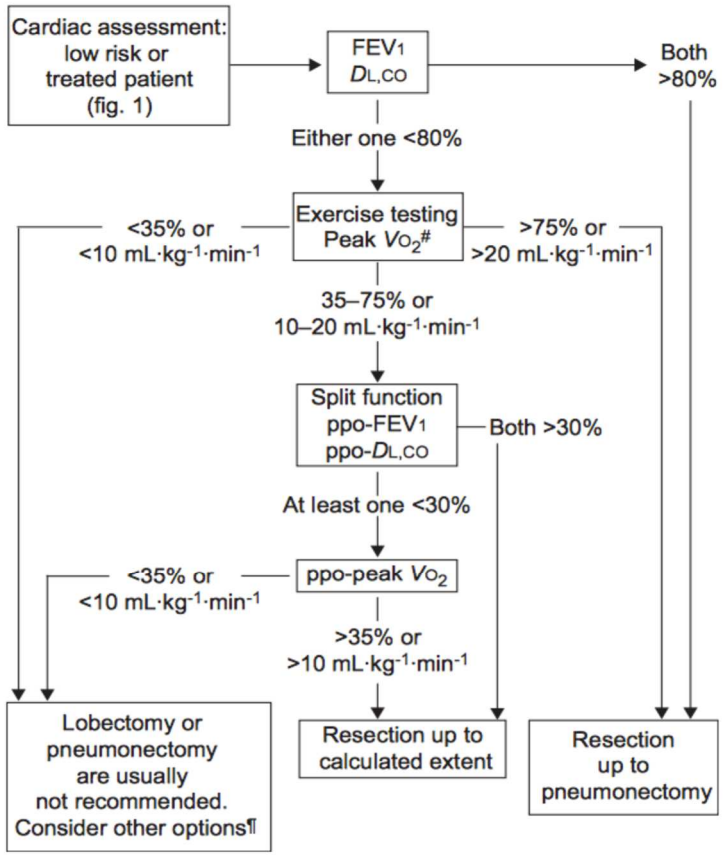
Class I	Patients have cardiac disease but without significant limitations of physical activity. Ordinary activity does not cause undue fatigue, palpitations, dyspnea (shortness of breath), or anginal pain.
Class II	Patients have slight limitations of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea or anginal pain.
Class III	Patients have marked limitations of physical activity. They are comfortable at rest, however less than ordinary physical activity results in fatigue, palpitations, dyspnea or anginal pain.
Class IV	Patients are unable to carry out any physical activity without symptoms referred to above. Some Class IV patients may have symptoms at rest.

Appendix 6 Process chart for mediastinal lymph node staging



Appendix 7 Process chart for lung function tests

Algorithm for the assessment of cardiopulmonary reserve before lung resection in lung cancer patients based on the ESTS guidelines [75]



FEV1: Force expiratory volume in 1 s.; $D_{L,CO}$: diffusing capacity of the lung for carbone monoxide; VO_2: oxygen comsumption; ppo: predictive postoperative

[#] if peak VO_2: is not available, cardiopulmonary exercice testing can be replaced by stair climbing; however, if altitude reaching stair climbing is < 22m, cardiopulmonary exercice testing with peak VO_2 measurement is highly recommended.

[¶] refer to guidelines

Appendix 8 Schedule of assessments and treatments

An adaptable scheduler is available on www.sakk.ch (→ Members → Trials → Lung Cancer → SAKK 16/14)

During trial treatment

	Pre-registration			R	Neoadjuvant chemotherapy									Neoadjuvant immunotherapy				SURGERY	Effective date
cycle [a]					1			2			3			1		2			
week (from start of trial therapy, i.e. chemotherapy cycle 1)					1	2	3	4	5	6	7	8	9	10	11	12	13	14 - 16	
day (from start of trial therapy, i.e. chemotherapy cycle 1)	-42 to 0	-28 to 0	-14 to 0	0	1	8	15	22	29	36	43	50	57	64	71	78	85	92 - 106	
month after surgery date																			
Neoadj. chemo.: cispatin (100 mg/m^2) + docetaxel (85 mg/m^2); +DXM d-1/d1/d2					x			x			x								
Neoadj. immunotherapy: MEDI4736 (750 mg)														x		x			
NSCLC pathologically confirmed and availability of tumor material (histology preferred, cytology accepted)	Prior registration																		
Informed consent for trial participation (incl. *optional* and mandatory TR) Informed consent for sample biobanking	Prior registration																		
Brain MRI or CT	x																		
Pulmonary function tests based on the ESTS guidelines	x																	x	
Echocardiography	x																		
PET/CT with contrast enhanced CT scan of thorax and upper abdomen		x										x [c]						x	
Tumor stage T1-3N2M0 (i.e. TNM 7th Edition: stage IIIA(N2)). Mediastinal lymph node staging acc. to Appendix 6		x																	
12-lead ECG (3x, 2-5 min apart)		x												x				x	
Medical history, including baseline symptoms, prev./concomitant corticosteroids, smoking habits, Charlson comorbidity index, etc.			x																
Physical examination, incl. WHO PS, weight, BP + at baseline: height			x x		x			x			x			x		x		x	
Vital signs (pre- during and post-infusion)														x		x			
Hematology [f]: Hemoglobin, neutrophils, platelets, WBC			x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Hepatic function [f]: AST/ALT; + at baseline: bilirubin, AP			x x		x			x			x			x	x	x	x	x	
Metabolic function (plasma or serum) [f]: Na, K, Mg			x		x			x			x			x	x	x	x	x	
Renal function [f]: serum creatinine + at baseline and during chemo: calculated creatinine clearance (Cockroft-Gault)			x x		x x			x x			x x			x	x	x	x	x	
Thyroid function [f]: TSH (free T3 & T4 if TSH abnormal)			x											x				x	
Urine analysis [f]: bilirubin, blood, glucose, ketones, pH, protein, specific gravity			x											x					
Coagulation parameters: PT, PTT, INR																		x	
Serum pregancy test (within 7 days before registration) [g]			x																
Mandatory TR: 30 ml heparin blood; 10 ml serum blood, 2.5 ml PAXgene blood			x [k]											x				x	
Optional TR: stool			x [k]																
AEs (incl. AESIs) / SAEs to be reported for 90 days after last dose of MEDI4736					x	x	x	x	x	x	x	x	x	x	x	x	x	x	

		Adjuvant immunotherapy [h]																											End of treatment
cycle [a]	Effective date surgery		1	2	3	4	5	6		7	8	9	10	11	12	13	14		15	16	primary endpoint: 12 mo since regi.	17	18	19		20	21	22	23	24	25	26	within 1 month after last dose
			4-6 wks after surgery																												Last cycle [b]	
month after surgery date [d]		1							4									7							10							
Adjuvant immunotherapy: MEDI4736 (750 mg)			x	x	x	x	x	x		x	x	x	x	x	x	x	x		x	x		x	x	x		x	x	x	x	x	x	x	
Contrast enhanced CT scan of thorax and upper abdomen [d]		x							x									x [e]			x [e]				x							
X-ray																																	x
12-lead ECG (3x, 2-5 min apart)			x									x																					x
Physical examination, incl. WHO PS, weight, BP			x	x	x	x	x	x		x	x	x	x	x	x	x	x		x	x		x	x	x		x	x	x	x	x	x	x	
Vital signs (pre- during and post-infusion)			x	x	x	x	x	x		x	x	x	x	x	x	x	x		x	x		x	x	x		x	x	x	x	x	x	x	
Hematology [f]: Hemoglobin, neutrophils, platelets, WBC			x		x		x			x		x		x		x			x			x		x			x		x		x		x
Hepatic function [f]: AST/ALT			x		x		x			x		x		x		x			x			x		x			x		x		x		x
Metabolic function (plasma or serum) [f]: Na, K, Mg			x		x		x			x		x		x		x			x			x		x			x		x		x		x
Renal function [f]: serum creatinine			x		x		x			x		x		x		x			x			x		x			x		x		x		x
Thyroid function [f]: TSH (free T3 & T4 if TSH abnormal)			x		x		x			x		x		x		x			x			x		x			x		x		x		x
Urine analysis [f]: bilirubin, blood, glucose, ketones, pH, protein, specific gravity			x		x		x			x		x		x		x			x			x		x			x		x		x		
Mandatory TR: 30 ml heparin blood; 10 ml serum blood, 2.5 ml PAXgene blood							x																										x [l]
Optional TR: stool							x [l]																										
AEs (incl. AESIs) / SAEs to be reported for 90 days after last dose of MEDI4736			x	x	x	x	x	x		x	x	x	x	x	x	x	x			x		x	x	x		x	x	x	x	x	x	x	x

[a] Refer to protocol sections 9 & 10 for the timelines of cycles, permitted delays, etc.
[b] Last cycle: after max. 1 year of adjuvant MEDI4736 (i.e. max.26 cycles) or at premature termination of adjuvant treatment
[c] Week 8 or 9
[d] CT scans have to be performed every 3 months (during adj. immunotherapy), starting 1 month after surgery
[e] If CT scan is within 6 weeks before EFS at 12 months (i.e. 12 months from registration), no need to repeat at 12 months - otherwise, it is imperative to repeat a CT assessment at 12 months [+ 4 weeks] from registration
[f] Assessments have to be done every other cycle during adjuvant MEDI4736
[g] For women in child-bearing age
[h] For patients undergoing RT: radiotherapy should start 4-6 weeks after surgery; the first infusion of adjuvant MEDI4736 should take place within 2 weeks after completion of radiotherapy
[i] In case end of treatment is due to recurrence during adj. immunotherapy: collect blood for mandatory TR and consider consenting the patient for optional TR (+ tumor re-biopsy/cytology)
[k] Baseline samples can be collected from 14 days prior registration until the first day of trial treatment (prior first dose of treatment)
[l] Stool Instruct the patient about stool collection at cycle for adjuvant MEDI4736 (refer also to protocol section 18.4)

After trial treatment

<table>
<tr><td colspan="3">Follow-up</td></tr>
<tr><td>Year 1-2</td><td>Year 3-5</td><td>Year 6 onwards</td></tr>
<tr><td>every 3 months</td><td>every 6 months</td><td>yearly</td></tr>
<tr><td colspan="3">Patient without recurrence
Physical examination</td></tr>
<tr><td colspan="2">Contrast enhanced thorax CT scan* alternating with chest X-ray
xx
*if patient is in FU without PD/relapse and prior to EFS at 12 months --> CT scan must be done at 1 year [+ 4 weeks] from registration</td><td>No imaging</td></tr>
<tr><td colspan="3">Patient after recurrence
Survival status & anti-cancer therapies</td></tr>
</table>