Investigational Drug	Durvalumab (MEDI4736) and Tremelimumab
Substance(s)	Durvalumab (MEDI4736), Tremelimumab, Docetaxel, Cisplatin, Carboplatin
Study Number	ESR-16-12356
Version Number	Version 1.5
Date	01.12.2020

First-line treatment of locally advanced HNSCC with double checkpoint blockade and radiotherapy dependent on intratumoral CD8+ T cell infiltration (CheckRad-CD8)

Sponsor: Dean of the Medical Faculty of the Friedrich-Alexander-Universität Erlangen-Nürnberg

PROTOCOL SYNOPSIS

Clinical Protocol

Study Title: First-line treatment of locally advanced HNSCC with double checkpoint blockade and radiotherapy dependent on intratumoral CD8+ T cell infiltration
Protocol Number: ESR-16-12356
Principal investigator: **PD Dr. Markus Hecht**
Scientific leadership: **Prof. Dr. Rainer Fietkau (Erlangen)** **Prof. Dr. Wilfried Budach (Düsseldorf)** **Prof. Dr. Claus Rödel (Frankfurt)** **PD Dr. Markus Hecht (Erlangen)** **Prof. Dr. Udo Gaipl (Erlangen)**
Biostatistics: **Dr. Axel Hinke (Düsseldorf, Cancer Clinical Research Consulting (CCRC))**
Clinical Phase: Phase II
Study Duration: 48 months
Study concept: All patients will initially be treated with one cycle of Cisplatin (30mg/m² d1-3) and Docetaxel (75mg/m² d1) and the PD-L1 inhibitor Durvalumab (1500mg absolute dose d5). Patients in the "Main Cohort" additionally receive the CTLA-4 Inhibitor Tremelimumab 75mg absolute dose (d5). Patients in the "Expansion Cohort 1" additionally receive Tremelimumab 300mg (d5) and patients in "Expansion Cohort 2" receive no Tremelimumab. Patients in the "Expantion cohort 1 or 2" should recive a single dose of pegylated G-CSF on d6. Treatment response will be evaluated clinically by endoscopy with biopsy. Changes of the CD8+ T cell density in the second biopsy compared to the first one before therapy will be used for patient selection. Patients with a stable or decreased CD8+ tumor infiltrating immune cell density or clinical progressive disease will receive standard CRT outside the trial. For these patients toxicity will be monitored until the first dose of the subsequent standard CRT. Patients with an increased CD8+ tumor infiltrating immune cell density and at least clinically stable disease will receive radioimmunotherapy with the PD-L1 Inhibitor Durvalumab (altogether 11 additional doses as concomitant and maintenance treatment). Patients in the "Main Cohort" will additionally receive Tremelimumab 75mg (altogether 3 additional dosis as concomitant and maintenance treatment). The primary endpoint of the "Main Cohort" is feasibility. Feasibility criteria are receiving the protocol treatment until cycle 6 of antibody treatment and absence of any of the DLT defined in the protocol. A feasibility rate of ≥80% is expected. The efficacy of radioimmunotherapy and predictive character of changes of CD8+ tumor infiltrating immune cells after induction chemo-immunotherapy are further endpoints. The follow up period will be two years after the completion of radiotherapy. In the "Expansion cohort 1 and 2" the endpoint will be toxicity.

Investigational products: Durvalumab (MEDI4736) will be supplied in glass vials containing 500 mg of liquid solution at a concentration of 50 mg/mL for intravenous (IV) administration. Tremelimumab is supplied as a sterile solution for IV infusion, filled in clear glass vials with a rubber stopper and aluminum seal. Each vial contains 20 mg/mL tremelimumab, in an isotonic solution at pH 5.5. Size of the vials is either nominal fill of 20ml (accounting to 400 mg/vial) or 1.25ml (accounting to 25 mg/vial). Radiotherapy will be delivered to the local tumor with linear accelerators as intensity modulated radiation therapy of volumetric modulated arc therapy.
Research Hypothesis Induction Chemo-Immuno-Therapy followed by Radio-Immuno-Therapy with durvalumab and tremelimumab after CD8-based patient selection is feasible and effective.
Objectives: **Primary Objectives:** Assessment of the feasibility of a new treatment scheme with induction Chemo-Immuno-Therapy followed by Radio-Immuno-Therapy Assessment of the predictive character of changes of CD8+ tumor infiltrating immune cells after induction chemo-immunotherapy **Secondary Objective(s)**: Assessment of the efficacy of a Radio-Immuno-Therapy with durvalumab and tremelimumab **Exploratory Objective(s):** Assessment of predictive value and changes of different tumor infiltrating immune cells and immunological tumor markers. Longitudinal analysis of the immune phenotype in the peripheral blood. Toxicity with enhanced or without CTLA-4 blockade (“Expansion Cohort 1 and 2”).
Study Design: Prospective, Open-Label, Non-Randomized
Number of Centers: 8
Number of Subjects: 120
Study Population: Patients with first treatment of locally advanced HNSCC (stage III-IVB).

Inclusion Criteria:

- Written informed consent and any locally-required authorization (e.g., HIPAA in the USA, EU Data Privacy Directive in the EU) obtained from the subject prior to performing any protocol-related procedures, including screening evaluations
- Age ≥ 18 years at time of study entry
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Locally advanced HNSCC, UICC stage III-IVB (oral cavity, oropharynx, hypopharynx, supraglottic larynx) (according to TNM version 8)
- Histological confirmation of HNSCC (regardless if p16 positive or negative)
- Measureable CD8 density in provided archival tumor tissue
- Body weight >30kg
- Adequate normal organ and marrow function as defined: Haemoglobin ≥ 9.0 g/dL; White blood cells (WBC) ≥ 3,000 per mm^3; Platelet count ≥100,000 per mm^3
- Serum bilirubin ≤ 1.5 x institutional upper limit of normal (ULN).
- AST (SGOT)/ALT (SGPT) ≤ 2.5 x institutional upper limit of normal (ULN)
- Creatinine Clearance >40ml/min (calculated from serum creatinine using the Cockcroft-Gault formula)
- Female subject of childbearing potential should have a negative serum pregnancy within 72 hours prior to receiving the first dose of durvalumab and tremelimumab. A highly sensitive pregnancy test must be used.
- Female subjects of childbearing potential must be willing to use a highly effective contraceptive measure as defined in the Clinical Trial Facilitation Group (CTFG) guideline ("Recommendations related to contraception and pregnancy testing in clinical trials.") For details see Section 7.1.1 of the study protocol. Highly effective contraception is required from screening to 90 days after the last dose of durvalumab monotherapy or 180 days after the last dose of durvalumab + tremelimumab combination therapy. (Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.)
- Male subjects of childbearing potential must agree to use a highly effective method of contraception as outlined in Section 7.1.1. Contraception, starting from screening to 90 days after the last dose of durvalumab monotherapy or 180 days after the last dose of durvalumab + tremelimumab combination therapy. (Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.)

- Subject 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.

Exclusion Criteria:

- Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)
- Participation in another clinical study with an investigational product during the last 4 weeks
- Concurrent enrolment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study
- Distant metastases
- Prior systemic anti-cancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumour embolization, monoclonal antibodies) of the locally advanced HNSCC
- Any other concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment, except the induction chemotherapy in the protocol. Concurrent use of hormonal therapy for non-cancer-related conditions (e.g., hormone replacement therapy) is acceptable
- Prior radiotherapy of HNSCC
- Radiotherapy to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of study drug
- Major surgical procedure of the current locally advanced HNSCC (as defined by the Investigator). Note: Local surgery of isolated lesions for palliative intent is acceptable.
- History of allogenic organ transplantation.
- Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc.]). The following are exceptions to this criterion:
    - Patients with vitiligo or alopecia areata
    - Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement
    - Any chronic skin condition that does not require systemic therapy
    - Patients without active disease in the last 5 years may be included but only after consultation with the study physician
    - Patients with celiac disease controlled by diet alone
- Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social

situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent

- History of another primary malignancy except for
  - Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of IP and of low potential risk for recurrence
  - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
  - Adequately treated carcinoma in situ without evidence of disease
- History of active primary immunodeficiency
- Active infection including **tuberculosis** (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), **hepatitis B** (known positive HBV surface antigen (HBsAg) result), **hepatitis C**, or **human immunodeficiency virus** (positive HIV 1/2 antibodies). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
- Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab or tremelimumab. The following are exceptions to this criterion:
  - Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra articular injection)
  - Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent
  - Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication)
- Receipt of live attenuated vaccine within 30 days prior to the first dose of IP. Note: Patients, if enrolled, should not receive live vaccine whilst receiving IP and up to 30 days after the last dose of IP.
- Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of durvalumab monotherapy or180 days after the last dose of durvalumab + tremelimumab combination therapy. This also applies to patients who receive only induction chemotherapy before the restaging endoscopy with biopsy.
- Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients.
- Prior randomisation or treatment in a previous durvalumab and/or tremelimumab clinical study regardless of treatment arm assignment.

- Known active bleeding diathesis.
- Past medical history of ILD, drug-induced ILD, radiation pneumonitis which required steroid treatment, or any evidence of clinically active interstitial lung disease.
- Judgment by the investigator that the patient is unsuitable to participate in the study and the patient is unlikely to comply with study procedures, restrictions and requirements.
- Known allergy or hypersensitivity to durvalumab, tremelimumab, cisplatin/carboplatin, docetaxel or any excipient
- Cisplatin/carboplatin induced polyneuropathy or hearing disorder

Investigational Product(s), Dose, and Mode of Administration:

"Main Cohort": Durvalumab 1500 mg plus tremelimumab 75 mg via IV infusion q4W for up to a maximum of 4 doses, followed by durvalumab monotherapy 1500mg via IV infusion q4W, starting 4 weeks after the infusion of the combination, for up to a maximum of 8 additional durvalumab doses.

"Expansion Cohort 1": Durvalumab 1500 mg plus tremelimumab 300 mg via IV infusion followed by durvalumab monotherapy 1500mg via IV infusion q4W, starting 4 weeks after the infusion of the combination, for up to a maximum of 11 additional durvalumab doses.

"Expansion Cohort 2": Durvalumab monotherapy 1500 mg via IV infusion q4W for up to a maximum of 12 durvalumab doses.

Study Assessments and Criteria for Evaluation:

Safety Assessments:

Toxicity will be documented according to CTCAE v4.03 before every administration of durvalumab/tremelimumab. An interim analysis will be performed after the first 20 patients have completed the radioimmunotherapy.

Efficacy Assessments:

PFS, OS and pathological confirmed response rate

Statistical Methods and Data Analysis:

The main objective of this phase II study is to assess, whether the experimental multimodal regimen at the chosen dosage shows a promising feasibility profile in the treatment of locally advanced HNSCC with immune reaction. The **feasibility rate** is chosen as primary safety endpoint, i.e. the proportion of patients receiving the protocol treatment according to the planned schedule (until cycle 6 of antibody treatment), without occurrence of at least one of the DLT events, as defined in full detail in section 6.3.3 of the protocol. This proportion will be presented with exact 90% and 95% confidence intervals.

The population for the primary endpoint, i.e. feasibility rate, is defined as follows (EAS):

- patients receiving the protocol treatment according to the planned schedule, until cycle 6 of antibody treatment, and
- patients in which any of the DLT events according to section 6.3.3 of the protocol was observed, irrespective of the overall amount and time schedule of treatment received.

All other safety and efficacy parameters will be evaluated in an explorative or descriptive manner, providing proportions, means, medians, ranges, standard deviations and/or confidence intervals, as appropriate. Subgroup analyses according to CD8+ cell changes will be performed, as well as historical comparisons on efficacy and safety to the results from the PacCis-RCT trial[1] (NCT01126216).

Sample Size Determination (Main Cohort):

Conventional empirical phase I study designs in clinical oncology assume, that an antineoplastic treatment is not feasible, if an unacceptable toxicity occurs in more than 1 out of 3 or 4 patients; however, the occurrence of dose limiting toxicities (DLT) in 1/6 is accepted. This leads to the conclusion that the limit of acceptance is considered to be around 20%.

A one-stage design for pilot studies according to Fleming (1982) is applied. In summary, the trial design is based on the following assumptions:

- The experimental therapy would be rated as unacceptable, if the actual feasibility rate (= 1 – rate with DLT events) was only 65% or lower.
- On the other hand, the therapy regimen would be considered to be a promising candidate for further development, if the true feasibility rate amounted to 80% or more.
- Probability to accept the experimental therapy as well tolerable, in spite of a true feasibility rate of < 65% (i.e. rate with DLT > 35%): 5% (type I error)
- Probability to reject the experimental therapy as not sufficiently feasible (<65%), although the true feasibility rate is promising (> 80%): 20% (type II error, corresponding to a power of 80%).

According to these parameters n = 56 patients evaluable for feasibility have to be recruited into the trial. In order to allow for about 50% with insufficient immune response, plus some non-informative drop-outs, a total number of 120 patients should be recruited. Recruitment is completed as soon as n= 56 patients entered radioimmunotherapy.

Sample Size Determinaiton Expansion Cohorts (Amendment 3 & 4):

The toxicity of two additional immune-oncologic treatment schemes with enhanced CTLA-4 blockade (Tremelimumab 300 mg Cx1) and without CTLA-4 blockade will be studied. For these toxicity analyses n= 20 patients should be recruited sequentially for each treatment scheme.

Schedule of study assessments: Screening and Treatment Period (12 months' treatment period for Durvalumab + Tremelimumab).

Trial Period:	**Pre-screening**	**Screening Phase**	**Treatment Cycles**								**Post-Treatment (max. 2 years after end of RT)**		
Treatment Cycle/Title:			Induction Chemo-Immuno	Re-staging 1	First RT[m]	2-4	last RT	5-6	Re-staging2 [p]	7-12	Safety Follow-up	Follow-up Visits (no progression)	Survival Follow-up (after progression)
Scheduling Window (Days):	-42 to -1	-28 to -1[a]	d1-5 (starting on Monday)	22-26	29 (or 36 or 43)	± 3		± 3	± 3	± 3	90 days post discon.	Every 12 weeks post discon.	Every 12 weeks
Documentation													
Informed Consent	X												
Inclusion/Exclusion Criteria		X											
Demographics and Medical History		X											
Alcohol / tobacco (past and present)		X											
ECOG Performance Status		X	X			X	X	X		X	X		
Concomitant Medication		X	X			X	X	X		X	X		
Review Adverse Events		X	X			X	X	X		X	X	X	
Post-study anticancer therapy status											X	X	
Survival Status													X
Patient questionnaires		X					X		X		X		
Treatment													
Chemotherapy Doc+Cis/Carbo			X										
Durvalumab administration			X			X		X		X			

Schedule of study assessments: Screening and Treatment Period (12 months' treatment period for Durvalumab + Tremelimumab).

Trial Period:	**Pre-screening**	**Screening Phase**	**Treatment Cycles**								**Post-Treatment (max. 2 years after end of RT)**		
Treatment Cycle/Title:			Induction Chemo-Immuno	Re-staging 1	First RT[m]	2-4	last RT	5-6	Re-staging2 [p]	7-12	Safety Follow-up	Follow-up Visits (no progression)	Survival Follow-up (after progression)
Scheduling Window (Days):	-42 to -1	-28 to -1[a]	d1-5 (starting on Monday)	22-26	29 (or 36 or 43)	± 3		± 3	± 3	± 3	90 days post discon.	Every 12 weeks post discon.	Every 12 weeks
Tremelimumab administration			X[q]			X[r]							
Examinations													
Full Physical Examination [k]		X					X				X		
Directed Physical Examination [k]			X		X	X		X	X	X		X	
Dental check-up		X											
Vital Signs and Weight		X	X[c]			X[c]	X	X[c]		X[c]	X		
12-lead ECG		X		X [b]									
Echokardiography		X											
contrast enhanced CT / MRI neck		X[h]							X			as indicated	
CT Thorax, CT/Sono Abdomen		X										as indicated	
Endoscopy with biopsy				X					X[o]				
Archival Tissue Collection	X[d]												
Assessment of CD8 density	X[d]			X									

Schedule of study assessments: Screening and Treatment Period (12 months' treatment period for Durvalumab + Tremelimumab).

Trial Period:	**Pre-screening**	**Screening Phase**	**Treatment Cycles**								**Post-Treatment (max. 2 years after end of RT)**		
Treatment Cycle/Title:			Induction Chemo-Immuno	Re-staging 1	First RT[m]	2-4	last RT	5-6	Re-staging2 [p]	7-12	Safety Follow-up	Follow-up Visits (no progression)	Survival Follow-up (after progression)
Scheduling Window (Days):	-42 to -1	-28 to -1[a]	d1-5 (starting on Monday)	22-26	29 (or 36 or 43)	± 3		± 3	± 3	± 3	90 days post discon.	Every 12 weeks post discon.	Every 12 weeks
Blood/Urine tests													
HIV, Hepatitis B/C test		X											
PT/INR and aPTT		X [n]		X [n]									
Highly sensitive serum pregnancy test [e]		X	X			X		X		X	X		
Urinalysis		X									X		
Hematology		X [f]	X[l]	X		X		X	X	X	X		
Comprehensive Serum Chemistry Panel		X	X[l]	X		X		X	X	X	X		
Thyroid function[g]		X	X	X		X		X	X	X	X		
Correlative Studies Blood Collection		X		X		X				X[i]	X		

RT: radiotherapy

[a] the screening phase can be prolonged for 7 days for radiotherapy treatment planning after consultation of the leading center

[b] ECG has to be performed before panendoscopy with biopsy

[c] subjects will have their blood pressure and pulse measured before, during, and after the infusion at the following times (based on a 60-minute infusion):

- At the beginning of the infusion (at 0 minutes)
- At 30 minutes during the infusion (±5 minutes)

Schedule of study assessments: Screening and Treatment Period (12 months' treatment period for Durvalumab + Tremelimumab).

Trial Period:	Pre-screening	Screening Phase	Treatment Cycles								Post-Treatment (max. 2 years after end of RT)		
Treatment Cycle/Title:			Induction Chemo-Immuno	Re-staging 1	First RT[m]	2-4	last RT	5-6	Re-staging2 [p]	7-12	Safety Follow-up	Follow-up Visits (no progression)	Survival Follow-up (after progression)
Scheduling Window (Days):	-42 to -1	-28 to -1[a]	d1-5 (starting on Monday)	22-26	29 (or 36 or 43)	± 3		± 3	± 3	± 3	90 days post discon.	Every 12 weeks post discon.	Every 12 weeks

- At the end of the infusion (at 60 minutes ±5 minutes)
- In the 1-hour observation period post-infusion: 30 and 60 minutes after the infusion (ie, 90 and 120 minutes from the start of the infusion) (±5 minutes) – for the first infusion only and then for subsequent infusions as clinically indicated

If the infusion takes longer than 60 minutes, then blood pressure and pulse measurements should follow the principles as described above or more frequently if clinically indicated.[d] after informed consent of the patient

[e] women of child bearing potential only. The highly sensitive serum pregnancy test will be performed in the screening phase and a maximum time period of 72 hours before each administration of durvalumab or tremelimumab during the whole treatment period. Pregnancy testing has to be continued monthly up to 90 days after durvalumab monotherapy or 180 days after durvalumab plus tremelimumab combination therapy.

[f] with differential CBC

[g] free T3 and free T4 will only be measured if TSH is abnormal. They should also be measured if there is clinical suspicion of an adverse event related to the endocrine system.

[h] a contrast enhanced CT neck should be performed between day -14 and -1 (basis for RECIST evaluation compared to radiotherapy planning CT)

[i] after the second restaging only at cycle 7 and 10

[k] in case of a previous history of bleeding or anticoagulant medications, each full or targeted physical examination has to include an oral inspection for bleeding signs and medical history of bleeding.

[l] after induction chemo-immunotherapy hematology and clinical chemistry have to be performed twice weekly during the following three weeks.

[m] Radiotherapy should start on d29. If not possible it can start delayed on d36 or d43 (if CD8 count is not completed and finally validated). In case of a delay the second administration of durvalumab + tremelimumab must also be delayed for one week or two weeks, respectively.

[n] coagulation parameters may be repeated as clinically indicated.

[o] in the panendoscopy after radio-immunotherapy a biopsy is only necessary if a residual primary tumor is suspected.

[p] Restaging 2 should be performed 12 weeks after last radiotherapy (irrespective of administered cycles of immunotherapy).

[q] "Main Cohort" and "Expansion Cohort 1"

[r] Only "Main Cohort"

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ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
AChE	Acetylcholine esterase
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
APF12	Proportion of patients alive and progression free at 12 months from randomization
AST	Aspartate aminotransferase
AUC	Area under the curve
$AUC_{0\text{-}28day}$	Area under the plasma drug concentration-time curve from time zero to Day 28 post-dose
AUC_{ss}	Area under the plasma drug concentration-time curve at steady state
BICR	Blinded Independent Central Review
BoR	Best objective response
BP	Blood pressure
BSA	Body surface area
C	Cycle
CD	Cluster of differentiation
CI	Confidence interval
CL	Clearance
C_{max}	Maximum plasma concentration
$C_{max,ss}$	Maximum plasma concentration at steady state
CR	Complete response
CRT	Chemoradiotherapy
CSA	Clinical study agreement

Abbreviation or special term	**Explanation**
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
CTLA-4	Cytotoxic T–lymphocyte-associated antigen 4
$C_{trough,ss}$	Trough concentration at steady state
CXCL	Chemokine (C-X-C motif) ligand
DLT	Dose Limiting Toxicities
DSMC	Data Safety Monitoring Committee
DoR	Duration of response
EAS	Evaluable analysis set
EC	Ethics Committee, synonymous to Institutional Review Board and Independent Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDoR	Expected duration of response
EGFR	Epidermal growth factor receptor
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
FFPE	Formalin-fixed-paraffin-embedded
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practice
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
HR	Hazard ratio
IB	Investigator's Brochure
IC	Immune cells

Abbreviation or special term	**Explanation**
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICI	Immune-Checkpoint-Inhibitors
ICRU	International Comission on Radiation Units and Measurements
IDMC	Independent Data Monitoring Committee
IFN	Interferon
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IL	Interleukin
ILD	Interstitial Lung Disease
ILS	Interstitial lung disease
IM	Intramuscular
imAE	Immune-mediated adverse events
IMT	Immunomodulatory therapy
IP	Investigational product
irAE	Immune-related adverse event
IRB	Institutional Review Board
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
ITT	Intent-to-Treat
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
mAb	Monoclonal antibody
MDSC	Myeloid-derived suppressor cell
MedDRA	Medical Dictionary for Regulatory Activities
MHC	Major Histocompatibility Complex
MHLW	Minister of Health, Labor, and Welfare
miRNA	Micro-ribonucleic acid

Abbreviation or special term	**Explanation**
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NE	Not evaluable
NSCLC	Non–small-cell lung cancer
OAE	Other significant adverse event
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
pCR	Pathological confirmed complete response
PD	Progressive disease
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PDx	Pharmacodynamic(s)
PFS	Progression-free survival
PFS2	Time to second progression
PGx	Pharmacogenetic research
PK	Pharmacokinetic(s)
PR	Partial response
PRO	Patient reported outcomes
q2w	Every 2 weeks
q3w	Every 3 weeks
q4w	Every 4 weeks
q6w	Every 6 weeks
q8w	Every 8 weeks
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
RIT	Radio-immun-therapy
RNA	Ribonucleic acid

Abbreviation or special term	**Explanation**
RR	Response rate
RT	Radiotherapy
RT-QPCR	Reverse transcription quantitative polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SD	Stable disease
SNP	Single nucleotide polymorphism
SoC	Standard of Care
sPD-L1	Soluble programmed cell death ligand 1
T_3	Triiodothyronine
T_4	Thyroxine
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US	United States
WBDC	Web-Based Data Capture
WHO	World Health Organization

1. INTRODUCTION

Head and neck squamous cell cancer (HNSCC) is frequently diagnosed after patients have noticed enlarged cervical lymph nodes. In this locally advanced stage, curative treatment options are chemoradiotherapy (CRT) or surgery followed by CRT. Recently, immunotherapy with a PD-1/PD-L1 pathway inhibitor improved overall survival in patients with metastatic HNSCC[2]. But in this trial the overall response rate was only 13% and stable disease was found in 23%. Thus, only a subgroup of the patients benefits from this immunotherapy. Several clinical trials with combinations of radio(chemo)therapy and immunotherapy were initiated in locally advanced HNSCC, but without adequate patient selection. Currently, there exists no reliable predictive parameter for patients that benefit from immunotherapy. In this trial the "endpoint" of the immune response, namely the infiltration of CD8+ T lymphocytes in the tumor, will be assessed as predictive marker for a radioimmunotherapy with dual immune checkpoint blockade.

1.1 Disease background

1.1.1 Radiochemotherapy of locally advanced HNSCC

Head and neck squamous cell cancer (HNSCC) is the 7th most common cancer worldwide. Approximately 60% of the patients are in an advanced stage of disease at the time of diagnosis[3]. The main risk factors are alcohol and tobacco. But also in non-smokers and non-drinkers these cancers appear. In many of these cases, especially in oropharyngeal cancer, an infection with the oncogenic human papilloma virus (HPV) is the responsible risk factor. The incidence of HPV positive oropharyngeal cancer varies in different countries.

In the locally advanced stage without distant metastases (UICC stage III-IVB) CRT or surgery followed by CRT are curative treatment options. As surgery is often not possible or causes too heavy morbidity, CRT is frequently performed. In large meta-analyses the addition of concomitant chemotherapy to radiotherapy, especially platinum-based, improved overall survival[4]. This effect is apparent in all locations of HNSCC[5]. Despite the combination of radiotherapy and chemotherapy, overall survival after 5 years was only 34% in this meta-analysis. The current standard of care is CRT with concomitant cisplatin or the combination of cisplatin and 5-flurouracil [6-8]. In more recent trials overall survival was improved up to 60%, probably due to improved radiation techniques and adverse event management [9,10].

A last approved agent in combination with radiotherapy was cetuximab. It improved overall survival compared to radiotherapy alone from 29 to 49 months[11]. But there exists only one trial and radiotherapy alone is no longer considered to be standard treatment. A comparison with CRT is still missing. A triple combination of cetuximab with cisplatin and radiotherapy did not

improve local tumor control or survival[9]. In a recent trial the kinase inhibitor lapatinib failed to prove efficacy in the adjuvant setting[12].

As mentioned above, HPV infection is an important risk factor for development of oropharyngeal squamous cell carcinoma (SCC). In clinical routine HPV infection is detected by p16 immunohistochemistry as there is a strong correlation. In oropharyngeal SCC p16 expression has a strong positive prognostic impact[13,14]. Positive p16 expression in combination with absence of smoking identifies the patient subgroup with the best prognosis after CRT[15].

In laryngeal preservation trials different treatment schedules were studied. Several trials with induction chemotherapy followed by radiotherapy or CRT were performed. Frequently used induction chemotherapy is the combination of docetaxel, cisplatin and 5-flurouracil (TPF). In a recent meta-analysis of five randomized trials with 2-3 cycles TPF induction no improved overall or progression free survival of induction chemotherapy before CRT was found[16]. However, single cycle induction chemotherapy is an appropriate method for patient selection. Patients responding to induction chemotherapy enter CRT and have a high rate of laryngeal preservation[17,18].

Concomitant chemotherapy not only improves survival, but also increases toxicity. The risk of acute mucositis and dysphagia is increased with concomitant chemotherapy[8]. With concomitant chemotherapy acute dysphagia grade 3-4 appears approximately in every second patient and late dysphagia grade 3-4 in every third patient[9]. Furthermore, approximately 20% of the patients suffer from hematologic toxicity grade 3-4 [8,9].

1.1.2 Immunotherapies

It is increasingly understood that cancers are recognized by the immune system, and, under some circumstances, the immune system may control or even eliminate tumors. Programmed death-ligand 1 (PD-L1) is a member of the B7 family of ligands that inhibit T-cell activity through binding to the PD-1 receptor[19] and to CD80[20]. PD-L1 expression is an adaptive response that helps tumors evade detection and elimination by the immune system. In contrast, cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) is constitutively expressed by regulatory T cells and upregulated on activated T cells. Binding of CTLA-4 to CD80 or CD86 on immune cells (IC) leads to inhibition of T-cell activation[21]. Expression of PD-L1 protein is induced by inflammatory signals that are typically associated with an adaptive immune response (e.g., IFNγ) and can be found on both tumor cells (TC) and tumor infiltrating IC. The binding of PD-L1 to PD-1 on activated T cells delivers an inhibitory signal to the T cells[22], preventing them from killing target TC, and protecting the tumor from immune elimination[23]. PD-L1 may also inhibit T cells through binding to CD80, although the exact mechanism is still not elucidated[20,24].

In vivo studies have shown that durvalumab inhibits tumor growth in xenograft models via a T cell-dependent mechanism[25].

PD-L1 is expressed in a broad range of cancers with a high frequency, up to 88% in some types of cancers. In some cancers, (e.g., renal cell carcinoma), taking into consideration the limitations of published literature the expression of PD-L1 seems associated with reduced survival and an unfavorable prognosis[26]. Further, radiation has been demonstrated to induce up-regulation of expression of PD-L1 on both, TC and dendritic cells[27]. Based on these findings, an anti-PD-L1 antibody could be used therapeutically to enhance antitumor immune responses in patients with cancer. Results of non-clinical and clinical studies of monoclonal antibodies (mAbs) targeting the PD-L1/PD-1 pathway have shown evidence of clinical activity and a manageable safety profile, supporting the hypothesis that an anti-PD-L1 antibody could be used to therapeutically enhance antitumor immune response in cancer patients[23,28-32] with responses that tend to be more pronounced in patients with tumors that express PD-L1[33-35]. In addition, high mutational burden e.g. in bladder carcinoma[36] may contribute to the responses seen with immune therapy.

The levels of tumor-infiltrating cells, and more specifically CD8+ cytotoxic T-cells, have been correlated to improved prognosis in a number of cancers including colorectal, melanoma, and lung cancers[37], suggesting that an anti-tumor immune response is beneficial to patients.

In contrast to PD-L1, cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) is constitutively expressed by regulatory T cells and upregulated on activated T cells. CTLA-4 delivers a negative regulatory signal to T cells upon binding of CD80 (B7.1) or CD86 (B7.2) ligands on antigen-presenting cells. In addition, blockade of CTLA-4 binding to CD80/86 by anti-CTLA-4 antibodies results in markedly enhanced T-cell activation and antitumor activity in animal models, including killing of established murine solid tumors and induction of protective antitumor immunity. Therefore, it is expected that treatment with an anti-CTLA-4 antibody will lead to increased activation of the human immune system, increasing antitumor activity in patients with solid tumors.

Pre-clinical data has now been added to with a wealth of clinical data showing that blockade of negative regulatory signals to T-cells such as cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed death ligand 1 (PD-L1) has promising clinical activity. Ipilimumab was granted United States (US) Food and Drug Administration (FDA) approval for the treatment of metastatic melanoma and is currently under investigation for several other malignancies whilst nivolumab and pembrolizumab, two anti-PD-1 agents and atezolizumab, an anti PD-L1 agent have been granted approvals by agencies such as the United States of America Food and Drug Administration and the European Medicines Agency approval for the treatment of a number of malignancies including metastatic melanoma, squamous and non-squamous cell non-small-cell lung cancer and urothelial carcinoma. In addition, data from agents in the anti-PD-1/PD-L1class shows clinical activity in a wide range of tumor types.

1.1.2 Immunotherapy in HNSCC

Recently, in the KEYNOTE-12 clinical trial the PD-1 inhibitor pembrolizumab was effective in second line therapy of metastatic head and neck squamous cell carcinoma (HNSCC). In this trial with 132 patients, the overall response rate to pembrolizumab was 18% and further 20% had stable disease. The overall survival rate after 6 months was 59%. In interpreting these results, it has to be considered, that 57% of the patients had at least two prior therapies. Interestingly, the responses to pembrolizumab were durable and the median duration of response was not reached (median follow-up duration 9 months)[38]. A similar PD-1 inhibitor nivolumab was tested in the CHECKMATE-141 trial as second line therapy against investigator's choice of chemotherapy. After 361 randomized patients this study was stopped because the PD-1 inhibitor significantly improved OS after 12 months from 17% to 36%. Interestingly, this overall survival benefit is based on a low overall response rate of only 13% and a stable disease in 23% of the patients[2]. These two PD-1 inhibitors have already been approved by the FDA for treatment of recurrent and or metastatic HNSCC after progression to platinum based chemotherapy. In a smaller trial containing 62 patients also treatment responses to the PD-L1 inhibitor Durvalumab were detected[35].

1.1.2 Durvalumab

Durvalumab is a human monoclonal antibody (mAb) of the immunoglobulin G (IgG) 1 kappa subclass that blocks the interaction of PD-L1 (but not programmed cell death ligand-2) with PD-1 on T cells and CD80 (B7.1) on IC. It is being developed by AstraZeneca/MedImmune for use in the treatment of cancer (MedImmune is a wholly owned subsidiary of AstraZeneca; AstraZeneca/MedImmune will be referred to as AstraZeneca throughout this document). Durvalumab has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity. *In vitro* studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells, resulting in their restored proliferation and release of interferon gamma (IFNγ)[35].

To date durvalumab has been given to more than 6900 patients as part of ongoing studies either as monotherapy or in combination with other anti-cancer agents. Details on the safety profile of durvalumab monotherapy are summarized in Section 5.3.4 and Appendix 1. . Refer to the current durvalumab Investigator's Brochure for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics.

1.1.3 Tremelimumab

Tremelimumab is a human immunoglobulin (Ig)G2 mAb that is directed against CTLA-4; cluster of differentiation [CD]152), a cell surface receptor that is expressed primarily on activated T cells and acts to inhibit their activation. Tremelimumab completely blocks the interaction of human CTLA-4 with CD80 and CD86, resulting in increased release of cytokines (interleukin [IL]-2 and interferon [IFN]-γ) from human T cells, peripheral blood mononuclear cells and whole blood[39]. Tremelimumab is being developed by AstraZeneca for use in the treatment of cancer.

To date tremelimumab has been given to more than 1000 patients as part of ongoing studies either as monotherapy or in combination with other anticancer agents. Refer to the current tremelimumab Investigator's Brochure for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics.

1.1.4 Durvalumab in combination with tremelimumab

Because the mechanisms of action of CTLA-4 and PD-1 are non-redundant targeting both PD-1 and CTLA-4 pathways may have additive or synergistic activity[35]; therefore, in addition to evaluating both agents in the monotherapy setting in a number of cancer indications AstraZeneca is also investigating the use of durvalumab + tremelimumab combination therapy for the treatment of cancer.

Study D4190C00006 is a Phase Ib dose-escalation study to establish the safety, PK/pharmacodynamics, and preliminary anti-tumor activity of durvalumab + tremelimumab combination therapy in patients with advanced NSCLC. The dosing schedule utilized is durvalumab every 2 or 4 weeks (Q2W, Q4W) up to 12 months, combined with tremelimumab Q4W up to Week 24 for 7 doses then every 12 weeks (Q12W) for 2 additional doses for up to 12 months. The study is ongoing and continues to accrue. In addition, other clinical studies have since started looking at the combination in both NSCLC and other oncology indications.

To date more than 800 patients have received the combination using a number of doses and dosing schedules. Details on the safety profile of durvalumab + tremelimumab combination therapy are summarized in the following sections. Refer to the current editions of the durvalumab and tremelimumab IBs for a complete summary of non-clinical and clinical information including safety, PK and efficacy.

1.1.5 Immunological effects of radiotherapy

Radiotherapy not only kills tumor cells, but also changes the tumor cell phenotype and the tumor microenvironment[40]. During the last decade a paradigm shift has taken place that besides the

direct or indirect interaction of ionizing radiation with the radiosensitive DNA also secondary radiation responses do occur in close proximity (bystander effect) or in distal sides of the irradiated area (non-targeted, systemic effect) [41]. Since the form of tumor cell death concomitantly with the release of danger signals by the stressed cells foster immune cell activation, distinct tumor cell death forms or phenotypically cell alterations do contribute to such non-DNA-targeted radiation-effects [42-44]. The so called immunogenic cancer cell death was mainly linked to certain chemotherapeutic agents such as anthracyclines [45] and has been expanded to many stressors like radiation during the last years [46,47]. A copious overview of the characteristics and detection of immunogenic cancer cell death is given in the recently published consensus guidelines on it [48]. The key outcome is that tumor cells should be killed in a way that they become an intrinsic cancer-specific vaccine [42,49].

RT is further capable of generating novel peptide sequences and enhances MHC class I expression [50]. Neoantigen-specific CD8+ T cell responses have been shown to go along with tumor regression [51]. Radiation further enhances the diversity of the T-cell receptor repertoire of intratumoral T cells [52]. Some of the mutations that create neo-antigens influence the response of patients to immune-checkpoint-inhibitors (ICI). In particular cytotoxic T lymphocytes that infiltrated the tumor and that are reactive to clonal neo-antigens often express high levels of PD-1. This indicates that even RT does induce CD8+ T cells against the tumor by generating neo-antigens, the consecutive high expression of PD-1 as immune suppressive molecule on the generated T cells counteracts the immune activating properties of RT and here strongly calls for combination with ICI [52-54]. Already in 2003 Honeychurch and colleagues demonstrated the CD8+T cells are key players in anti-tumor immunity induced by radiation in combination with immunotherapy [55].

The immune-mediated anti-tumor mechanisms induced by RT may vary in the irradiated tumor compared to non-irradiated tumor masses. Abscopal effects of radiation, first described by R.H. Mole in 1953, describe an effect/action at a distance from the irradiated volume but within the same organism [56], nowadays often referred to radiotherapy-induced responses outside the radiation field. However, abscopal responses after RT are rarely seen in clinics and it appears that potentiating the immune response may be of benefit in distant control [57,58]. In 2004 Demaria and colleagues demonstrated in pre-clinical mouse models that the abscopal effect of RT is observed only when additional immune stimulation is ensured and that it is mediated by the adaptive immune system [59]. In a prospective clinical trial with radiotherapy and granulocyte-macrophage colony-stimulating factor, systemic effects of local radiotherapy (10x3.5Gy) were achieved in 11 of 41 patients with different solid tumors[60].

1.1.6 Combination of Radiotherapy with Immune-checkpoint-Inhibitors

Programmed cell death ligand 1 (PD-L1) is the ligand of PD-1 and can be found on cancer cells and immune cells. In a meta-analysis of different tumor entities high cancer cell PD-L1

expression was associated with an improved response rate to inhibitors of PD-1 or PD-L1[61]. In the CHECKMATE-141 trial in HNSCC the PD-1 inhibitor nivolumab especially improved overall survival in the PD-L1 positive subgroup[2]. The PD-1 inhibitor pembrolizumab and the PD-L1 inhibitor durvalumab showed similar effects in HNSCC[38]. *In vitro* radiotherapy induces an up-regulation of PD-L1[62,63]. This up-regulation has recently been confirmed in cancer patients, when PD-L1 status was compared before and after radiotherapy[64,65]. In preclinical experiments fractionated radiotherapy induced a stronger up-regulation of PD-L1 than a single high dose[63]. The maximal increase of PD-L1 was detected three days after fractionated radiation *in vitro*[62].

In preclinical experiments the combination of radiotherapy and PD-1/PD-L1 pathway blockade improved local tumor control[27,62,66]. This effect bases on the induction of anti-tumor immunity. Consequently, also metastases distant from the irradiated tumor responded after radiotherapy and the survival rate of the animals improved[27,62]. Thus, local radiotherapy, acting as *in situ* vaccination, is probably able to improve not only local but also systemic tumor control in combination with PD-1/PD-L1 pathway blockade. In melanoma patients these systemic effects of radiotherapy combined with PD-1/PD-L1 pathway blockade have already been reported[67].

These immunological effects of local radiotherapy have frequently been reported in patients in combination with anti-CTLA4 therapy in different tumor entities[68-70]. In a retrospective analysis of 21 melanoma patients with progression under anti-CTLA4, local radiotherapy re-induced a systemic treatment response in more than half of the patients[71]. This was not dependent of the location of the irradiated metastasis. In another retrospective clinical analysis of patients treated with CTLA-4 blockade shrinkage of not irradiated index lesions occurred more frequently if radiotherapy and immunotherapy was administered within 3 months compared to longer time intervals[72]. In a further retrospective study survival after stereotactic radiosurgery of brain metastases was better with concomitant CTLA-4 blockade compared to sequential treatment[73].

Recently, the combination of radiotherapy with PD-1/PD-L1 and CTLA-4 blockade was studied precisely in a preclinical setting. [74]. In these extensive preclinical experiments a strong synergism of this triple therapy was confirmed. The authors concluded a model, in which radiotherapy induced a repertoire diversity of T cell receptors through an increased antigen presentation of dying tumor cell. CTLA-4 blockade induced the maturation of these T-cells and increased the CD8/Treg ratio. The final step was to overcome T cell exhaustion by PD-L1 blockade. This synergism finally led to an oligo-clonal expansion of cytotoxic T-cells. Consequently, there is a strong preclinical rationale to combine radiotherapy with PD-L1 and CTLA-4 blockade.

1.2 Research hypothesis

5-year overall survival after CRT of locally advanced HNSCC is still only 40-60%. Recently, PD-1/PD-L1 pathway blockade proved to be an efficient treatment in metastatic HNSCC[2,38]. The response rate to this treatment is low, but responses are durable. So far, there is no reliable predictive marker available. In this trial the safety of a radioimmunotherapy with combined PD-L1/CTLA-4 blockade will be studied. After an induction immunotherapy patient selection for radioimmunotherapy bases on infiltration of CD8+ immune cells in the tumor. This is the "endpoint" of anti-tumor immunity and correlates with the treatment response[75]. With this study concept, an adequate patient selection for radioimmunotherapy without concomitant chemotherapy should be possible. The main hypothesis is that concomitant radiotherapy with dual immune checkpoint blockade is feasible with acceptable toxicity. Furthermore, a radioimmunotherapy may improve tumor control in this selected patient collective, which is a secondary hypothesis.

1.3 Rationale for conducting this study

1.3.1 Rationale for study population

As discussed above overall survival rate for locally advanced HNSCC after CRT is still only 40-60%. The survival advantage of a concomitant chemotherapy is approximately 6,5% after 5 years[4]. However, chemotherapy also induces hematologic toxicity grade 3-4 in 20% of the patients [8,9]. Furthermore, it increases acute dysphagia grade 3-4 appears approximately in every second patient and late dysphagia grade 3-4 in every third patient[9]. PD-1 inhibitors improve OS in metastatic HNSCC in a randomized trial[2]. However, the response rate in this trial was only 13% and 23% had stable disease. The OS benefit bases on durable responses of these patients. Thus, a subgroup of patients extremely benefits from immunotherapy with PD-1 inhibitors. For future trials, it is essential to find an adequate predictive marker to identify these patients and allow an anti-PD1 treatment in earlier stages of the disease. In the trial comparing a PD-1 inhibitor in metastatic HNSCC with chemotherapy, toxicity was lower and patient reported quality of life higher in the immunotherapy arm[2]. Thus, radioimmunotherapy is probably less toxic than the standard CRT.

1.3.2 Rationale for induction chemo-immunotherapy before radiotherapy as patient selection

As mentioned above there exists no reliable predictive marker for the success of PD-1/PD-L1 pathway blockade in HNSCC. Treatment response is independent from HPV status. PD-L1 has a weak predictive character in metastatic HNSCC. But the response rate in PD-L1 positive

(≥1%) patients is only between 17-19% compared to 12-16% in PD-L1 negative (<1%) patients[2,38]. Another method for patient selection is frequently used in laryngeal preservation trials. Patients receive one cycle of induction chemotherapy and the clinical response to this treatment is evaluated. Patients responding to induction chemotherapy have a high local control rate of approximately 85%[17]. Consequently, an induction immunotherapy might be effective to predict treatment response to radioimmunotherapy. However, approximately half of the patients develop progressive disease after PD-1/PD-L1 pathway blockade[2,38]. This cannot be accepted in a curative setting in locally advanced HNSCC. Furthermore, tumor shrinkage after successful immunotherapy occurs later compared to chemotherapy. This would require a long induction period. Consequently, in this trial induction phase chemotherapy, which has a response rate of approximately 80%[17], is combined with immunotherapy. This prevents disease progression in many patients. Due to this combined treatment, the response to immunotherapy cannot be evaluated by tumor shrinkage. Alterations of the density of tumor infiltrating CD8+ immune cells are used instead. This is the "endpoint" of the anti-tumor immune response and correlates with treatment response to PD-1/PD-L1 pathway blockade[75]. In lung cancer neoadjuvant chemotherapy did influence neither PD-L1 expression nor the tumor infiltrating immune cells[76]. Consequently, alterations of the density of CD8+ tumor infiltrating immune cells is a probably suitable future predictive parameter. The time interval of 4 weeks between induction immunotherapy and evaluation of CD8+ tumor infiltrating immune cells is expected to be long enough. In a phase II clinical trial in patients with HNSCC one cycle of pembrolizumab 1-3 weeks before surgery led to a pathological response (>10% tumor effect) in 47% of the 19 evaluated patients[77]. In a clinical trial in lung cancer the addition of pembrolizumab to platinum-based chemotherapy significantly improved the response rate and progression free survival[78].

1.3.3 Rationale for Durvalumab + tremelimumab combination therapy

1.3.3.1 Rationale for Durvalumab + Tremelimumab treatment scheme selection

The durvalumab + tremelimumab doses and regimen selected for this study are based on the goal of selecting an optimal combination dose of durvalumab and tremelimumab that would yield sustained target suppression (sPD-L1), demonstrate promising efficacy, and have an acceptable safety profile.

The "Main Cohort" of the trial received Durvalumab 1500mg fix dose Q4W (12 cycles) and Tremelimumab 75mg fix dose Q4W (4 cycles). In the EAGLE trial (Licitra L, ASCO 2019, Abstract 6012) the combination of Durvalumab+Tremelimumab was not superior to Durvalumab monotherapy in second line treatment of recurrent and/or metastatic HNSCC [79]. In

this trial Tremelimumab dosing was 1mg/kg body weight for four doses. The survival curve for the combined treatment tended to be below the monotherapy curve, but without gaining statistical significance. Consequently, it was decided to study a Tremelimumab dosing of most likely more efficient combination regimen of Durvalumab 1500 mg Q4W plus Tremelimumab 300 mg (only single dose) in "Expansion Cohort 1". In addition the "Expansion Conort 2" studies Durvalumab without additional Tremelimumab.

Pharmacokinetics (PK) / Pharmacodynamics data "Main Cohort" (dosing before amendment 3)

Study D4190C00006 included dose cohorts with both a Q4W and a Q2W schedule of durvalumab in combination with a Q4W schedule of tremelimumab. The Q4W schedule was included to align with the Q4W dosing of tremelimumab. PK simulations from durvalumab monotherapy data indicated that a similar area under the plasma drug concentration-time curve at steady state (AUC_{ss}; 4 weeks) was expected following both 10 mg/kg Q2W and 20 mg/kg Q4W dosing with durvalumab. The observed durvalumab PK data from the D4190C00006 study were in line with the predicted monotherapy PK data developed pre-clinically and in line with that seen in the first-time-in-human (FTIH), single agent study (CD-ON-MEDI4736-1108) in patients with advanced solid tumors. This demonstrates similar exposure of durvalumab 20 mg/kg Q4W and 10 mg/kg Q2W, with no alterations in PK when durvalumab and tremelimumab (doses ranging from 1 to 3 mg/kg) are dosed together. While the median maximum plasma concentration at steady state ($C_{max,ss}$) is expected to be higher with 20 mg/kg Q4W (approximately 1.5 fold) and median trough concentration at steady state ($C_{trough,ss}$) is expected to be higher with 10 mg/kg Q2W (approximately 1.25 fold), this is not expected to impact the overall safety and efficacy profile, based on existing preclinical and clinical data.

Monotonic increases in PDx activity were observed with increasing doses of tremelimumab relative to the activity observed in patients treated with durvalumab monotherapy. There was evidence of augmented PDx activity relative to durvalumab monotherapy with combination doses containing 1 mg/kg tremelimumab, inclusive of both, the 15 and 20 mg/kg durvalumab plus 1 mg/kg tremelimumab combinations.

Pharmacokinetics (PK) / pharmacodynamics data "Expansion Cohorts" (dosing after amendment 3)

The supporting data for the regimen in "Expansion Cohort 1" are based on PK and pharmacodyamic data from regimens that used tremelimumab doses of greater than 1 mg/kg from Study D4190C00006 (ClinicalTrials.gov Identifier: NCT02000947). An approximate dose-proportional increase in PK exposure (maximum serum concentration and area under the serum drug concentration-time curve from time 0 to Day 28 post-dose) was observed with increasing doses of tremelimumab (1, 3, and 10 mg/kg). An exploratory pharmacodynamic analysis bioanalytically evaluated the effects of tremelimumab on proliferating T-cells from

NSCLC patients who received tremelimumab (1, 3, or 10 mg/kg) and durvalumab (15 or 20 mg/kg) combination treatment. Monotonic increases in pharmacodynamics activity with the combination (increased activation/ proliferation markers on CD4 and CD8 T cells in periphery) were observed with increasing doses of tremelimumab (1, 3, 10 mg/kg). The peak increase (%) from baseline of CD4+Ki67+ T-cells was observed 8 days post administration, and the peak level was significantly increased ($p \leq 0.05$) as increasing dose of tremelimumab in the range of 1 to 10 mg/kg. Study data also suggested that higher peak exposure (maximum serum concentration [Cmax]) of tremelimumab is related to a higher maximum pharmacodynamics effect in the NSCLC patient population. Overall, the PK/pharmacodynamic data suggest that tremelimumab of dose greater than 1 mg/kg with a higher peak exposure may be associated with a higher pharmacodynamic effect.

Additionally, based on simulation data, the Cmax (78 μg/mL) post single dose administration of tremelimumab 4 mg/kg is approximately 4-fold higher than the predicted Cmax (19 μg/mL) post the first dose of tremelimumab 1 mg/kg, and is 3-fold higher than the predicted Cmax (25 μg/mL) post the fourth dose of tremelimumab 1 mg/kg in a Q4W×4 doses setting.

Clinical data "Main Cohort" (dosing before amendment 3)

In Study D4190C00006 various dose combinations have been explored, with doses of tremelimumab ranging from 1 to 10 mg/kg and doses of durvalumab ranging from 3 to 20 mg/kg. Tremelimumab was given on a Q4W schedule whilst durvalumab was explored in both a Q4W and Q2W schedule, with the goal of identifying the dose combination that best optimizes the risk: benefit profile in an acceptable range of PK and pharmacodynamic values.

Patients treated with doses of tremelimumab above 1 mg/kg had a higher rate of adverse events (AEs), including discontinuations due to AEs, serious AEs (SAEs), and severe AEs. Between the 10 mg/kg durvalumab + 1 mg/kg tremelimumab and 10 mg/kg durvalumab + 3 mg/kg tremelimumab cohorts treated at the q2w schedule, the number of patients reporting any AE, Grade 3 AEs, SAEs, and treatment-related AEs was higher in the 10 mg/kg durvalumab + 3 mg/kg tremelimumab cohort than the 10 mg/kg durvalumab + 1 mg/kg tremelimumab cohort. A similar pattern was noted in the q4w regimens, suggesting that, as the dose of tremelimumab increased above 1 mg/kg, a higher rate of treatment-related events may be anticipated. Further, the SAEs frequently attributed to immunotherapy, pneumonitis and colitis, were more commonly seen in cohorts using either 3 or 10 mg/kg of tremelimumab compared to the 1-mg/kg dose cohorts. Together, these data suggest that a combination using a tremelimumab dose of 1 mg/kg appeared to minimize the rate of toxicity when combined with durvalumab. As a result, all combination doses utilizing either the 3 or 10 mg/kg doses of tremelimumab were eliminated in the final dose selection.

In contrast, cohorts assessing higher doses of durvalumab with a constant dose of tremelimumab did not show an increase in the rate of AEs. The data suggested that increasing doses of durvalumab may not impact the safety of the combination as much as the tremelimumab dose. Further, safety data between the 10-mg/kg and 20-mg/kg cohorts were similar, with no change in safety events with increasing dose of durvalumab.

In Study D4190C00006, of all treatment cohorts, the cohort of patients treated in the 20 mg/kg durvalumab + 1 mg/kg tremelimumab group had a tolerable safety profile, but still showed strong evidence of clinical activity. No dose-limiting toxicities (DLTs) were reported in this cohort.

Preliminary clinical activity of the durvalumab and tremelimumab combination did not appear to change with increasing doses of tremelimumab. The 15- and 20-mg/kg durvalumab q4w cohorts demonstrated objective responses at all doses of tremelimumab, and increasing doses of tremelimumab did not provide deeper or more rapid responses.

Efficacy data suggested that the 20 mg/kg durvalumab + 1 mg/kg tremelimumab dose cohort may demonstrate equivalent clinical activity to other dose combinations. Of the 14 patients in this cohort, there were 4 patients (29%) with PR, 4 patients (29%) with SD, and 2 patients (14%) with PD. Two patients were not evaluable for response.

Altogether, the data suggested that a 20 mg/kg durvalumab + 1 mg/kg tremelimumab dose combination should be selected for further development.

Refer to the current durvalumab Investigator's Brochure for a complete summary of non-clinical and clinical information on the durvalumab + tremelimumab combination, including safety, efficacy and pharmacokinetics.

Clinical data "Expansion Cohorts" (dosing after amendment 3)

"Expansion cohort 1":

A single dose of tremelimumab 4 mg/kg, while maintaining a similar overall exposure, has a 3- to 4-fold higher Cmax compared to the 4 doses of tremelimumab 1 mg/kg. Therefore, this single administration of the higher dose of tremelimumab may have the potential for better anti-tumor activity while potentially avoiding any cumulative toxicity associated with repeated dosing of the 1 mg/kg tremelimumab.

In the Phase I/II study (Study D4190C00022, ClinicalTrials.gov Identifier: NCT02519348) evaluating the tolerability and clinical activity of durvalumab and tremelimumab in advanced HCC patients who progressed on, are intolerant of, or refused sorafenib-based therapy, durvalumab (1500 mg Q4W) as a single agent and in combination with two dosing regimens of tremelimumab (75 mg Q4W X 4 doses or 300mg X 1 dose) were evaluated. In the pre-planned

interim analysis, safety data showed that both combination dose regimens were tolerable and no new safety signals were identified. While efficacy for durvalumab in combination with tremelimumab at the 75mg dose (Q4W X 4) was not meaningfully better than durvalumab monotherapy, efficacy data supports continued evaluation of durvalumab in combination with tremelimumab at the 300mg dose (X1).

"Expansion Cohort 2":

As mentioned above the phase III EAGLE trial that randomized durvalumab monotherapy versus durvalumab+tremelimumab (4 combined doses) versus second line chemotherapy failed to prove superiority of immunoncologic treatment schemes[79]. Regarding second line chemothearpy the hazard ratio for death was 1.04 for durvalumab+tremelimumab, but tended to be improved with 0.88 for durvalumab monotherapy. The survival rate after 12 months was equal (30.4% vs. 30.5%) for durvalumab+tremelimumab and second line chemotherapy, but also tended to be superior for durvalumab monotherapy (37.0%). Consequently, the "Expansion Cohort 2" with durvalumab monotherapy was designed in the CheckRad-CD8 trial, as this may also be a promising combination scheme for future trials.

1.3.3.2 Rationale for number of cycles of combination therapy followed by durvalumab monotherapy

Long-term follow up on melanoma patients treated with ipilimumab, an anti-CTLA-4 targeting antibody (dosed every 3 weeks [q3w] for 4 doses and then discontinued), shows that patients responding to ipilimumab derive long-term benefit, with a 3-year OS rate of approximately 22%. Furthermore, the survival curve in this population reached a plateau at 3 years and was maintained through 10 years of follow up[80].

Similar data have been presented for other anti-PD-1/PD-L1 targeting antibodies:

Nivolumab (anti-PD-1) was dosed q2w for up to 96 weeks in a large Phase I dose-escalation and expansion study, and showed responses were maintained for a median of 22.94 months for melanoma (doses 0.1 mg/kg to 10 mg/kg), 17 months for NSCLC (doses 1, 3, and 10 mg/kg), and 12.9 months for renal cell carcinoma patients (doses 1 and 10 mg/kg) at the time of data analysis. Furthermore, responses were maintained beyond treatment discontinuation in the majority of patients who stopped nivolumab treatment (either due to protocol specified end of treatment, complete response [CR], or toxicity) for up to 56 weeks at the time of data analysis[81] MPDL3280a (anti-PD-L1) and the combination of nivolumab with ipilimumab, in which patients were dosed for a finite time period and responses maintained beyond treatment discontinuation have been reported[82].

Similar long term results may be expected with use of other immune-mediated cancer therapeutics including anti-CTLA-4 antibodies such as tremelimumab, anti PD-L1 antibodies such as durvalumab, or the combination of the two.

As mentioned above, due to more recent data from durvalumab+tremelimumab combination trials (EAGLE-trial, Study D4190C00006, Study D4190C00022), this is studied in "Expansion Cohort 1" after amendment 3. In "Expansion Cohort 1" the durvalumab + tremelimumab combination regimen will be administered for 1 dose followed by durvalumab monotherapy Q4W for up to a maximum further 11 doses. "Expansion cohort 2" will study durvalumab monotherapy Q4W for 12 doses.

1.3.3.3 Rationale for fixed dosing

A population PK model was developed for durvalumab 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 (WT) on the PK of durvalumab (coefficient of ≤ 0.5). The impact of body WT-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) of durvalumab was evaluated by comparing predicted steady state PK concentrations (5th, median and 95th percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body WT of ~75 kg). A total of 1000 patients were simulated using body WT distribution of 40–120 kg. Simulation results demonstrate that body WT-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 1 through Phase 3 (N=654; doses= 0.01 to 15 mg/kg Q4W or Q90D; metastatic melanoma)[83]. Population PK model indicated minor impact of body WT on PK of tremelimumab (coefficient of ≤ 0.5). The WT-based (1 mg/kg Q4W) and fixed dosing (75 mg/kg Q4W; based on median body WT of ~75 kg) regimens were compared using predicted PK concentrations (5th, median and 95th percentiles) using population PK model in a simulated population of 1000 patients with body weight distribution of 40 to 120 kg. Similar to durvalumab, simulations indicated that both body WT-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[84-87]. 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[86]. 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[87].

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 switch to fixed dosing regimens. Based on average body WT of 75 kg, a fixed dose of 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) and a fixed dose

of 75 mg Q4W tremelimumab (equivalent to 1mg/kg Q4W) was chosen for the "Main Cohort". As mentioned above, more recent data support a tremelimumab dosing of a single cycle of 300mg fix dose. This dosing will be used for the "Expansion Cohort 1".

1.3.4 Rationale for radiotherapy + durvalumab + tremelimumab combination

As mentioned above radiotherapy not only kills tumor cells, but also changes the tumor cell phenotype and the tumor microenvironment[35]. This can support the induction of an anti-tumor immune response, but also leads to up-regulation of checkpoint-molecules. There exist preclinical data for combined blockade of the PD-1/PD-L1 and the CTLA-4 pathway and radiotherapy[74]. The basic mechanism is that radiotherapy increases the diversity of the T-cell receptor repertoire of intratumoral T cells. CTLA-4 blockade promotes the expansion of T cells. Finally, PD-L1 blockade helps to overcome T-cell exhaustion. This triple combination was highly effective in animal models. Regarding the time schedule of radiotherapy and PD-1/PD-L1 pathway blockade a concomitant treatment was most effective in preclinical models[62]. The time point of immunotherapy will always be Friday of the first radiotherapy week. This prevents that radiotherapy impedes an upcoming immune response due to the usual radiotherapy interruption on Saturday and Sunday.

1.3.5 Rationale for the non-randomized study design

This is a non-randomized trial with feasibility as primary endpoint. After induction chemo-immunotherapy, patients with an increased infiltration of CD8+ intratumoral immune cells enter radioimmunotherapy. This requires endoscopy with biopsy before and after induction therapy. Patients with stable or decreased CD8 density are treated with standard CRT outside the trial and only their survival will be followed up. This group cannot be used as control group, as CD8+ tumor infiltrating cells are a relevant prognostic parameter of HNSCC[88,89]. Due to this patient selection, no randomization is possible. A treatment of the CRT patients inside the trial just as safety control group cannot be justified. The margins for the safety analysis will be fixed in the protocol before the trial starts.

1.3.6 Rationale for study endpoints

The primary endpoint of the trial is the feasibility of a radioimmunotherapy. The feasibility rate of the radioimmunotherapy should be at least 80%. It is suspected, that toxicity is lower than in a standard CRT. Recently, our study group completed the PacCis-RCT trial (NCT01126216) in locally advanced HNSCC, which includes a standard CRT arm. The toxicity of the radioimmunotherapy in this trial will be compared to the standard CRT arm of the PacCis-RCT trial. PFS, OS and pathological confirmed response rate are further secondary endpoints and will be compared to the results of the PacCis-RCT trial[1]. The study will not be powered for these endpoints. Further exploratory analyses include changes of the tumor microenvironment and peripheral blood immune status after induction chemo-immunotherapy. These analyses may

give more information on the mechanism of immunotherapy in combination with chemotherapy and radiotherapy and may help to improve future treatment schemes.

1.4 Benefit/risk and ethical assessment

1.4.1 Potential benefits

1.4.1.1 Durvalumab + tremelimumab

Recently, the PD-1 inhibitor nivolumab improved overall survival in metastatic HNSCC compared to chemotherapy[2]. In this trial, toxicity was lower in the immunotherapy arm than in the chemotherapy arm. This overall survival benefit was highly significant despite a low overall response rate of only 13%. The overall response rate of pembrolizumab in metastatic HNSCC was 18%[38]. A combined PD-1/PD-L1 blockade combined with CTLA-4 blockade was studied in metastatic melanoma. The combination of nivolumab with Ipilimumab improved the overall response rate to 58% compared to 44% with nivolumab alone and consequently also the progression free survival[90] .

1.4.1.2 Induction chemo-immunotherapy before radiotherapy

In this trial an induction chemo-immunotherapy is used for patient selection. So far, the best predictive parameter is PD-L1. However, PD-L1 has only a weak predictive character in metastatic HNSCC, as the response rate in PD-L1 positive (≥1%) patients is only between 17-19% compared to 12-16% in PD-L1 negative (<1%) [2,38]. In this trial only patients with an increased CD8+ tumor infiltrating immune cell density after induction immunotherapy will be treated with radioimmunotherapy. Tumor infiltrating CD8+ immune cells are the "endpoint" of the immune response and correlate with the response rate to PD-1/PD-L1 pathway blockade[75]. As immunotherapy alone may lead to disease progression in every other patient in the induction period, it is combined with one cycle induction chemotherapy. Induction chemotherapy with Cisplatin/Docetaxel leads to a tumor shrinkage in approximately 80% of the patients[17].

1.4.1.3 Radiation + Durvalumab + Tremelimumab

Combined PD-1/PD-L1 pathway and CTLA-4 blockade had an excellent overall response rate of 58% in metastatic melanoma[90]. Radiotherapy changes the tumor cell phenotype and the tumor microenvironment towards a more inflamed pattern[40]. In preclinical experiments, this triple combination was highly effective[74]. This combined radioimmunotherapy after adequate patient selection as described above should lead to excellent tumor control. Furthermore, the concomitant chemotherapy of the standard CRT, not only induced hematologic toxicity but also increases local radiation dermatitis and dysphagia[9]. Approximately a quarter of the patients suffer from hematologic toxicity grade 3 or higher[9]. Furthermore, the concomitant chemotherapy increases the risk or dermatitis and mucositis[8]. In metastatic HNSCC the toxicity

of the PD-1 inhibitor Nivolumab was lower than the toxicity of chemotherapy. Thus, radioimmunotherapy will probably help to spare toxicity in these selected patients.

1.4.2 Identified and potential risks

Monoclonal antibodies directed against immune checkpoint proteins, such as PD-L1 as well as those directed against PD-1 or CTLA-4, aim to boost endogenous immune responses directed against tumor cells. By stimulating the immune system however, there is the potential for adverse effects on other tissues.

Most adverse drug reactions seen with the immune checkpoint inhibitor class of agents are thought to be due to the effects of inflammatory cells on specific tissues. Potential risks are events with a potential inflammatory mechanism and which may require more frequent monitoring and/or unique interventions such as immunosuppressants and/or endocrine replacement therapy. These risks include gastrointestinal AEs such as colitis and diarrhoea, pneumonitis, nephritis and acute renal failure, hepatic AEs such as hepatitis and liver enzyme elevations, dermatitis, and endocrinopathies such as hypo- and hyper-thyroidism, hypophysitis and adrenal insufficiency.

1.4.2.1 Durvalumab

Identified risks with durvalumab are cough/productive cough, pneumonitis, ILD, dysphonia, ALT/AST increased, hepatitis, diarrhoea, abdominal pain, colitis, hypothyroidism, hyperthyroidism, blood TSH increased, blood TSH decreased, adrenal insufficiency, Type 1 diabetes mellitus, hypophysitis/hypopituitarism, diabetes insipidus, blood creatinine increased, dysuria, nephritis, rash, pruritus, night sweats, dermatitis, myocarditis, pyrexia, oedema peripheral, upper respiratory tract infections, pneumonia, oral candidiasis, dental and oral soft tissue infections, influenza, myalgia, myositis, polymyositis and infusion-related reaction. Further information on these risks can be found in the current version of the durvalumab IB.

Additional potential risks include: pancreatitis. Rare events as pericarditis, sarcoidosis, uveitis, and other events involving the eye (eg. keratitis and optic neuritis), skin (eg. scleroderma and vitiligo), and haematological (eg. haemolytic anaemia and immune thrombocytopenic purpura), rheumatological events (polymyalgia rheumatic and autoimmune arthritis) and neuropathy/neuromuscular toxicities (eg, myasthenia gravis, Guillain Barre syndrome). Hypersensitivity reactions including Anaphylaxis and allergic reaction, cytokine release syndrome, immune complex disease). Other infections.

In monotherapy clinical studies AEs (all grades) reported very commonly (≥ 10% of patients) are fatigue, nausea, decreased appetite, dyspnea, cough, constipation, diarrhea, vomiting, back

pain, pyrexia, abdominal pain, anemia, arthralgia, peripheral edema, headache, rash, and pruritus. Approximately 10% of patients experienced an AE that resulted in permanent discontinuation of durvalumab and approximately 3.5% of patients experienced an SAE that was considered being related to durvalumab by the study investigator.

The majority of treatment-related AEs were manageable with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicity (see the Dosing Modification and Toxicity Management Guidelines).

A detailed summary of durvalumab monotherapy AE data can be found in the current version of the durvalumab IB.

1.4.2.2 Tremelimumab

Identified risks with tremelimumab are diarrhea, rash, and pruritus.

Potential risks based on the mechanism of action of tremelimumab and related molecules (ipilimumab) include potentially immune-mediated reactions including: gastrointestinal events eg. colitis, intestinal perforation, abdominal pain, dehydration, nausea and vomiting, and decreased appetite; dermatitis including urticaria, skin exfoliation, and dry skin; endocrinopathies including hypophysitis, adrenal insufficiency, and hyper- and hypothyroidism; hepatic events including hepatitis, and liver enzyme elevations; pancreatitis and lipase and amylase elevation; pneumonitis; nervous system events including encephalitis, peripheral motor and sensory neuropathies, Guillain-Barre and myasthenia; cytopenias including thrombocytopenia, anemia and neutropenia and infusion-related reactions, anaphylaxis, and allergic reactions. Further information on these risks can be found in the current version of the tremelimumab IB.

In monotherapy clinical studies AEs (all grades) reported very commonly (≥ 10% of patients) were diarrhea, fatigue, nausea, rash, pruritus, decreased appetite, vomiting, pyrexia, cough, constipation, abdominal pain, headache, dyspnea, and decreased weight. Approximately 10% of patients experienced an AE that resulted in permanent discontinuation of tremelimumab and approximately 20% of patients experienced an SAE that was considered being related to tremelimumab by the study investigator.

A detailed summary of tremelimumab monotherapy AE data can be found in the current version of the tremelimumab IB.

1.4.2.3 Durvalumab + Tremelimumab

The safety of durvalumab + tremelimumab combination therapy is being evaluated in the ongoing dose escalation and dose expansion Study 006, in patients with NSCLC, and has so far shown a manageable safety and tolerability profile.

The identified risks with the combination of durvalumab + tremelimumab are similar to those for durvalumab and tremelimumab monotherapy. Additional risks include: increase of amylase/ lipase, intestinal perforation and large intestine perforation.

Emerging data from study 006 and from combinations of other agents in the same class indicate an increased frequency and/or severity of some of these potential immune-mediated toxicities.

In durvalumab + tremelimumab combination studies AEs (all grades) reported very commonly (≥ 10% of patients) are diarrhea, fatigue, nausea, dyspnea, pruritus, rash, increased amylase, decreased appetite, pyrexia, increased ALT, cough, colitis, and increased lipase.

Approximately 27% of patients experienced an AE that resulted in permanent discontinuation of study drug and approximately 73% of patients experienced an SAE that was considered to be related to durvalumab and tremelimumab by the study investigator.

A detailed summary of durvalumab + tremelimumab combination AE data can be found in the current version of the durvalumab IB.

1.4.2.4 Docetaxel + Cisplatin / Carboplatin

One cycle of induction chemotherapy with Docetaxel (75mg/m² day1) and Cisplatin (30mg/m² day 1-3) is usually tolerated well[91]. A commonly reported AE of this treatment scheme (≥ 10% of patients) is hematologic toxicity (all grades of leucopenia, thrombocytopenia or anemia). This induction chemotherapy has already been studied[92]. In an analysis of toxicity only 1/25 patients developed a clinical relevant leukocytopenia in the induction phase without use of prophylactic G-CSF. Consequently, the administration of this chemotherapy treatment scheme became clinical routine without prophylactic G-CSF. Other commonly reported AEs of cisplatin are renal dysfunction, nausea, vomiting, diarrhea, hearing disorders, hyperuricemia or renal toxicity. Neurotoxicity is rare. Patients will receive antiemetic premedication and sufficient hydration before drug administration. The hydration can lead to edema or decreased potassium, sodium, calcium or magnesium. Patients with impaired kidney function (creatinine clearance <60ml/min) or cardiac function insufficient for hydration will receive Carboplatin instead of Cisplatin. Besides hematologic toxicity, commonly reported AEs (≥ 10% of patients) of Carboplatin are nausea, vomiting, abdominal pain, elevated liver blood parameters or decreased potassium, sodium, calcium or magnesium. In addition, neurotoxicity or ototoxicity can appear.

Commonly reported AEs of Docetaxel are hematologic toxicity, nausea, vomiting, stomatitis, diarrhea and asthenia. Other possible AEs are neurotoxicity, local phlebitis (puncture) or hypersensitivity.

1.4.2.5 Radiotherapy

A standard radiotherapy will be performed. Commonly reported acute AEs ≥3° of radiotherapy alone are skin reactions (23%), mucositis/stomatitis (56%) and dysphagia (31%)[11]. Supportive care will be performed with mouthwash, nurturing unguents, analgesic medication and nutrition via feeding tube (PEG; percutaneous endoscopic gastrostomy). In case of a bacterial superinfection antibiotic therapy will be started. More severe complications as bleeding are rare and will be treated surgical if necessary. Other possible adverse events taste disorders or xerostomia.

Durable late complications include xerostomia, fibrosis or edema of the neck. Fibrosis of the pharyngeal muscles will lead to dysphagia. Fibrosis of the skin or subcutaneous tissue can reduce the mobility of the neck. Another possible complication is gnathospasm. More severe late complications as mandibular osteoradionecrosis or carotid artery stenosis are extremely rare. A dental check is necessary in all patients in the screening phase to reduce the risk of osteoradionecrosis.A further late complication is hypothyroidism, which might require hormone substitution therapy.

1.4.2.6 Radiotherapy + Durvalumab + Tremelimumab

As mentioned above concomitant chemotherapy increases local toxicity of radiotherapy. Theoretically, also immunotherapy with Durvalumab and Tremelimumab may increase local toxicity of radiotherapy. However, so far no cases of increased radiosensitivity of patients treated with immune-checkpoint-inhibitors have been reported. One overlapping late toxicity is hypothyroidism, which appears both in radiotherapy and in durvalumab monotherapy (without or with tremelimumab). In combined treatment, the frequency and severity is probably increased. In case of clinically relevant hypothyroidism, hormone substitution is necessary. Similarly, also skin- and mucosal toxicity leading to swallowing problems might be increased in combined treatment. But recently, in the randomized GORTEC 2015-01 trial radiotherapy of locally advanced HNSCC with pembrolizumab was compared to radiotherapy with cetuximab[93]. The rate of severe (grade 3+) mucositis and dermatitis was lower in the pembrolizumab arm. Own clinical experience of six patients treated with combined PD-1 and CTLA-4 blockade (Ipilimumab and Nivolumab) and radiotherapy of different locations also revealed no increased toxicity (unpublished data). In addition, an increase of immune related toxicity by radiotherapy may be possible. As mentioned above radiotherapy can also induce immunological effects acting on tumor cells distant from the irradiated metastasis (abscopal

effect). Theoretically, this effect may also appear in healthy tissue, but this has never been reported so far.

1.4.3 Overall benefit: risk

The main risks of Tremelimumab + Durvalumab + Radiotherapy are immunological AEs caused by Tremelimumab + Durvalumab. However, the safety of this combination has already been studied in clinical trials with altogether at least 800 patients. The most common AE was diarrhea. Other AEs included fatigue and skin reactions. More severe AEs as pneumonitis were rare. Refer to the current editions of the durvalumab and tremelimumab IBs for a complete summary of non-clinical and clinical information including safety, PK and efficacy. In this trial an induction chemotherapy with Docetaxel + Cisplatin or Carboplatin will be used. However, only one cycle is administered compared to 3 cycles in laryngeal preservation trials. One cycle induction chemotherapy is usually tolerated very well. The endoscopy with second biopsy after induction treatment is clinical standard in laryngeal preservation approaches and usually not associated with severe toxicity. A standard radiotherapy will be performed. Due to modern radiation techniques used in this trial toxicity is probably lower than reported in the previous trials above. As reported above, concomitant chemotherapy increases local toxicity of radiotherapy. This effect may also appear with concomitant immunotherapy. In retrospective analyses grade 3-4 toxicity was increased neither for the combination of radiotherapy with CTLA-4 blockade[73,94] nor for the combination with PD-1 blockade[67,95]. Also for the combination or durvalumab with radiotherapy in a small analysis of 15 radiotherapies in 10 patients no grade 3-4 toxicity appeared[96]. Consequently, in patients treated with radioimmunotherapy toxicity is probably lower than in patients treated with standard CRT. PD-1/PD-L1 pathway blockade induced durable responses in metastatic HNSCC in a patient subgroup. Combined PD-1/CTLA-4 blockade had extraordinarily high response rates in metastatic melanoma. In this trial a better patient selection based on the “endpoint” of an immune response may help to identify patients responding to immunotherapy. One potential risk may be the omission of the concomitant chemotherapy during radiotherapy. The combination of cisplatin/5FU is frequently used as concomitant treatment. Combination chemotherapy with cisplatin/5FU has a response rate of 20%[97]. Recently, in the HAWK trial durvalumab monotherapy was tested in recurrent/metastatic HNSCC. The response rate was 16.2%. A limitation of this study is that all patients were PD-L1 positive. But in the planned trial patients receive platinum-based chemotherapy before immunotherapy. In a recent analysis in HNSCC patients, platinum-based chemotherapy increased PD-L1 expression in 69% of prior PD-L1 negative patients[98]. In the planned trial patients additionally receive the CTLA4-Inhibitor tremelimumab, which is expected to increase the response rate. As mentioned above, this has been shown for nivolumab plus ipilimumab in melanoma patients. Furthermore, chemotherapy is not completely omitted in this trial, as all patients receive on cycle of induction

chemotherapy. Based on this intensified immunotherapy, induction chemotherapy and patient selection, we expect a real benefit for the patients treated with radioimmunotherapy. Patients treated with radioimmunotherapy will probably have better tumor control after radioimmunotherapy and less adverse events than patients treated with standard CRT.

2. STUDY OBJECTIVE

2.1.1 Primary objective(s)

The feasibility of a radioimmunotherapy with durvalumab and tremelimumab will be studied in locally advanced HNSCC. A feasibility rate of 80% is expected. Toxicity will be reported according to CTCAE 4.0.

The predictive character of changes of CD8+ tumor infiltrating immune cells after induction chemo-immunotherapy will be studied. It is expected that approximately every other patient has an increased density of CD8+ tumor infiltrating immune cells after induction chemo-immunotherapy (see section: 11.3 Determination of sample size).

2.1.2 Secondary objective(s)

The efficacy of a radioimmunotherapy with durvalumab and tremelimumab will be studied in locally advanced HNSCC. As secondary endpoints PFS, OS and the pathologically confirmed response rate were chosen. As this is a single arm trial, results will be compared to published studies and especially the PacCis-RCT trial (NCT01126216), which was recently completed by the same study group. In this trial the 3-year PFS was 58% and the 3-year OS 64% [1]. It is expected that efficacy is not lower than with standard CRT. Furthermore, the response rate after the induction chemo-immunotherapy will evaluate by RECIST 1.1 criteria.

2.1.3 Exploratory objective(s)

A multiparameter and multislice assay (15 makers) of paraffin-embedded tumor tissue will be performed to analyze the immunomodulatory potential of the tumor infiltrating immune cells and to get first hints about the functional activity of the antigen presenting cells and cytotoxic cells. These analyses will be complemented with an interferon gamma response gene signature. This may help to identify better future predictive parameters. In a closely-meshed longitudinal analysis, the detailed immune phenotype of the peripheral blood during chemo-immunotherapy and radioimmunotherapy will be studied and for available time points compared to the events inside the tumor tissue. This multicolor flow cytometry-based assay includes at least the monitoring of 34 immune cell and 3 non-immune cell subsets, cell morphology and additional activation markers, including all major immune cells in peripheral blood[99]. These analyses will be complemented with a peripheral blood cell free DNA evaluation method, which may become a useful tool for tumor assessment in future.

3. STUDY DESIGN

3.1 Overview of study design

Cell density of CD8+ T cells will be evaluated in the biopsy before therapy. All patients will initially be treated with the PD-L1 inhibitor Durvalumab and the CTLA-4 Inhibitor Tremelimumab ("Main Cohort" 75mg, "Expansion Cohort 1" 300mg, "Expansion Cohort 2" no Tremelimumab) and one cycle with Cisplatin (30mg/m² d1-3) and Docetaxel (75mg/m² d1). Treatment response will be evaluated clinically by endoscopy with biopsy. In patients with impaired creatinine clearance (<60ml/min) Carboplatin will be used instead of cisplatin. Patients should recive a single dose of pegylated G-CSF on d6 (only "Expansion Cohorts", after amendment 3). Changes of the CD8+ T cell density in the second biopsy compared to the first one before therapy will be used for patient selection. There will be no randomization. Patients with a stable or decreased CD8+ tumor infiltrating immune cell density or clinical progressive disease will receive standard CRT or salvage surgery outside the trial and only their survival status will be followed up. For these patients toxicity will be monitored until the first dose of the subsequent standard CRT. Patients with an increased CD8+ tumor infiltrating immune cell density and at least clinically stable disease will receive radioimmunotherapy with subsequent maintenance therapy with the PD-L1 inhibitor Durvalumab (altogether 12 doses q4w including the induction dose). Patients in the "Main Cohort" will additionally receive three doses of Tremelimumab 75mg q4w. Patients with pathologically confirmed complete response (pCR) of their primary tumor will also receive radioimmunotherapy (irrespective of cervical lymph nodes). Restaging will be performed twelve weeks after radiotherapy, i.e. after six doses of immune checkpoint inhibitor therapy (week 23 in the schedule). Imaging of the neck will be performed with contrast enhanced CT and/or MRI. In addition a panendoscopy and, if clinically indicated, a biopsy is taken. Alternatively an FDG-PET/CT can be done if this is clinical routine in the treating center. In this case a panendoscopy with biopsy is only necessary, if local tumor persistence at the primary site is suspected. Patients with complete response will receive additional 6 cycles of durvalumab maintenance treatment. If there is residual persistent disease in the neck, a neck dissection is recommended. The extent of the neck dissection is at the discretion of the treating head and neck surgeon. In case of histologically confirmed local tumor persistence, salvage surgery should be planned at the discretion of the treating head and neck surgeon, if the patient is fit for the planned intervention and accepts the intervention and its potential side effects. Surgical specimens with residual tumor are to be submitted to the reference pathology at the university hospitals Erlangen. If a complete tumor resection is possible with salvage surgery, the patient should also receive further 6 cycles of durvalumab maintenance treatment. In case of major surgery, the time period from the last durvalumab administration should be at least one week. After surgery, durvalumab maintenance should only

be started when the wound healing is completed. In case of delayed wound healing durvalumab can be administered delayed up to 4 weeks (time period of one cycle). The following time intervals up to cycle 6 will be the usual q4w. In case of a longer delay, the principal investigator has to be contacted. If a complete tumor resection is not possible, the systemic treatment has to be changed. The decision which systemic treatment should be offered outside this trial is at the discretion of the treating physician and depends on the fitness of the patient. A possible treatment outside this trial for fit patients would be the EXTREME scheme (Cisplatin/5FU/Cetuximab). During the treatment in this trial, in order not to impede the immune stimulation, glucocorticoids will be used restrictively. The primary endpoint is the feasibility. The efficacy of radioimmunotherapy and predictive character of changes of CD8+ tumor infiltrating immune cells after induction chemo-immunotherapy are further endpoints. The follow up period will be two years after the completion of radiotherapy.

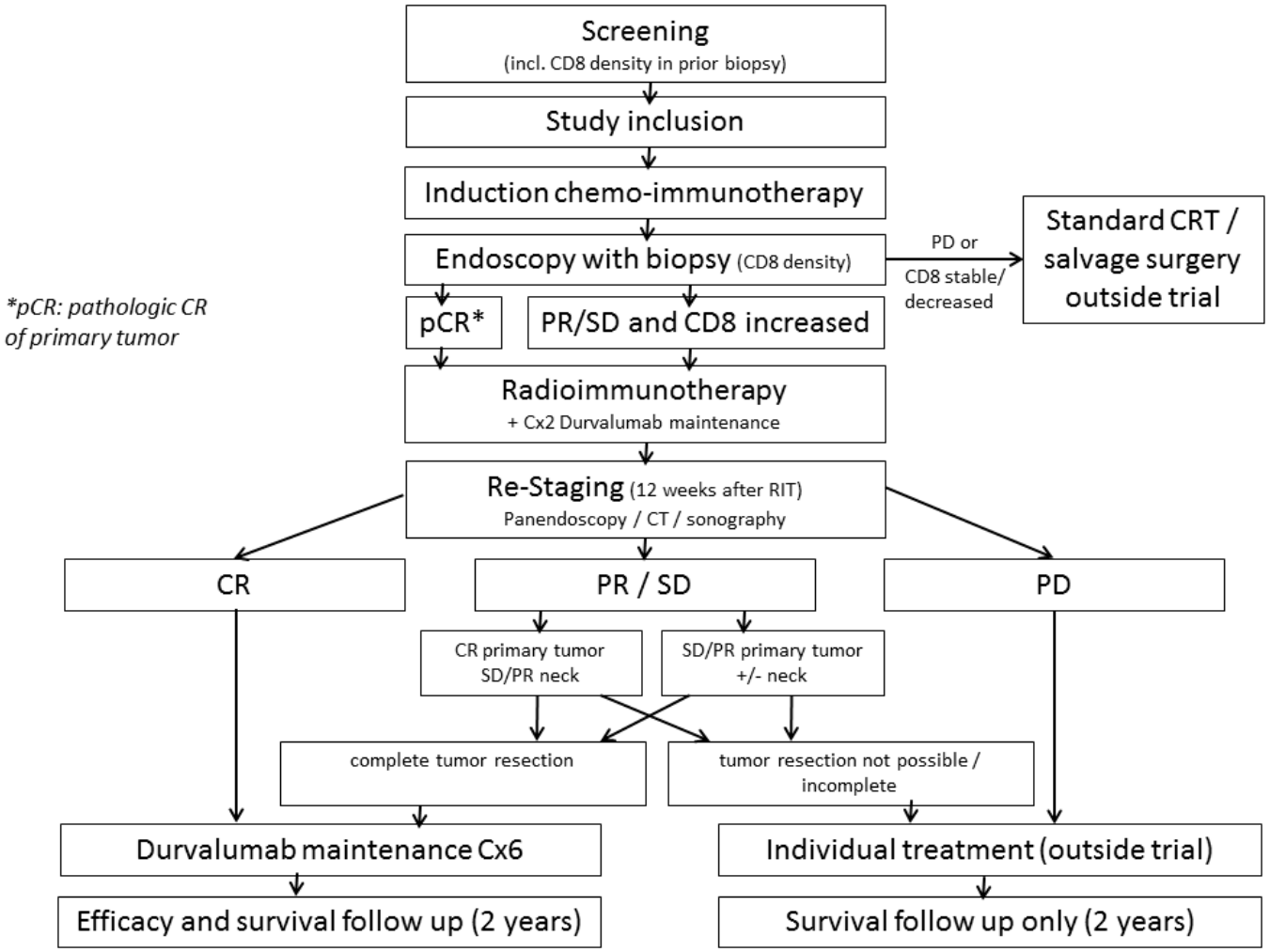
3.2 Study scheme

Clinical Study Protocol

Drug Substance Durvalumab (MEDI4736), Tremelimumab, Docetaxel, Cisplatin, Carboplatin

Study Code ESR-16-12356; Edition Number Version 1.5; Date 01.12.2020

Figure 1. Study flow chart

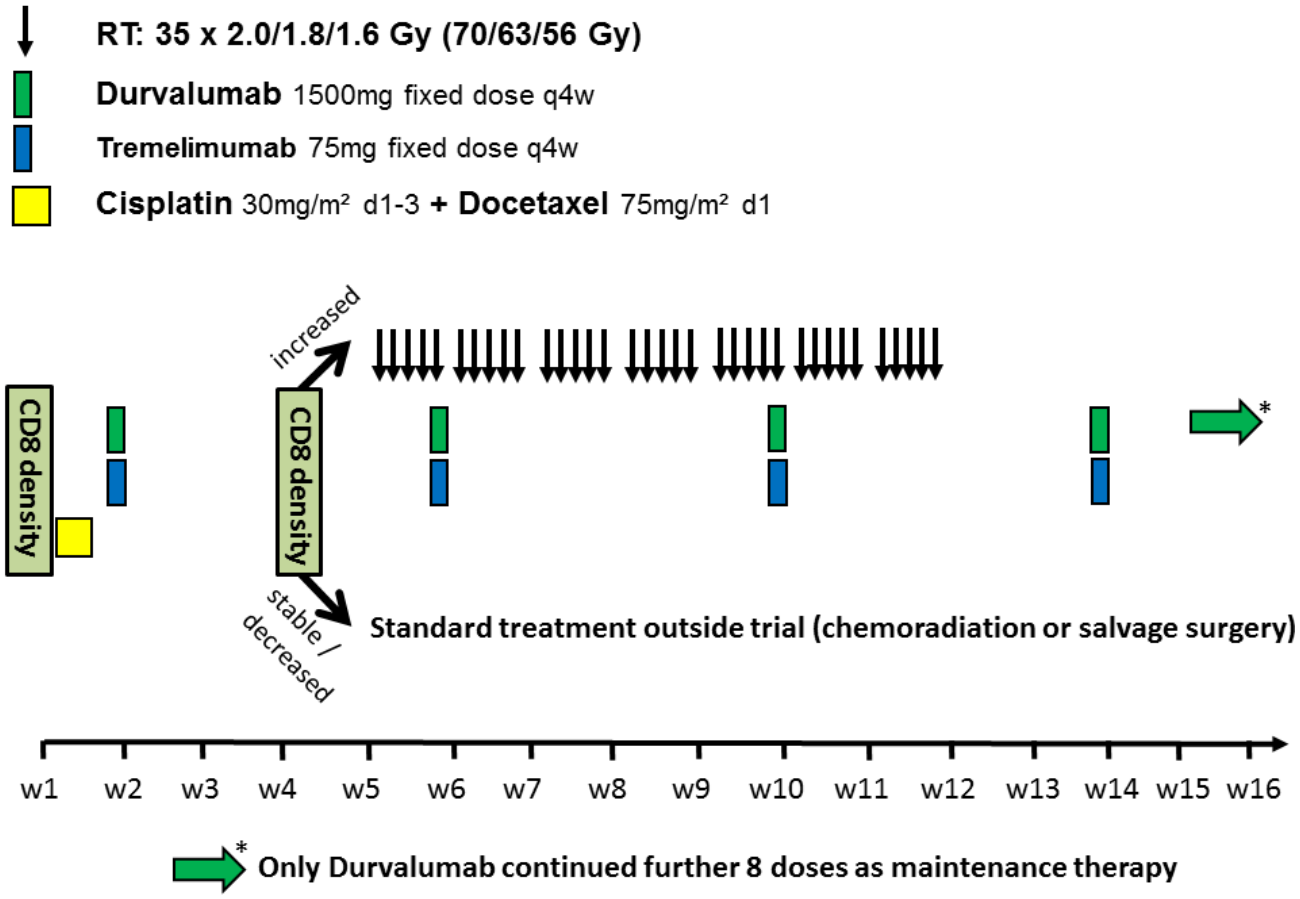


Clinical Study Protocol

Drug Substance Durvalumab (MEDI4736), Tremelimumab, Docetaxel, Cisplatin, Carboplatin

Study Code ESR-16-12356; Edition Number Version 1.5; Date 01.12.2020

Figure 2. A: Treatment flow chart "Main Cohort"

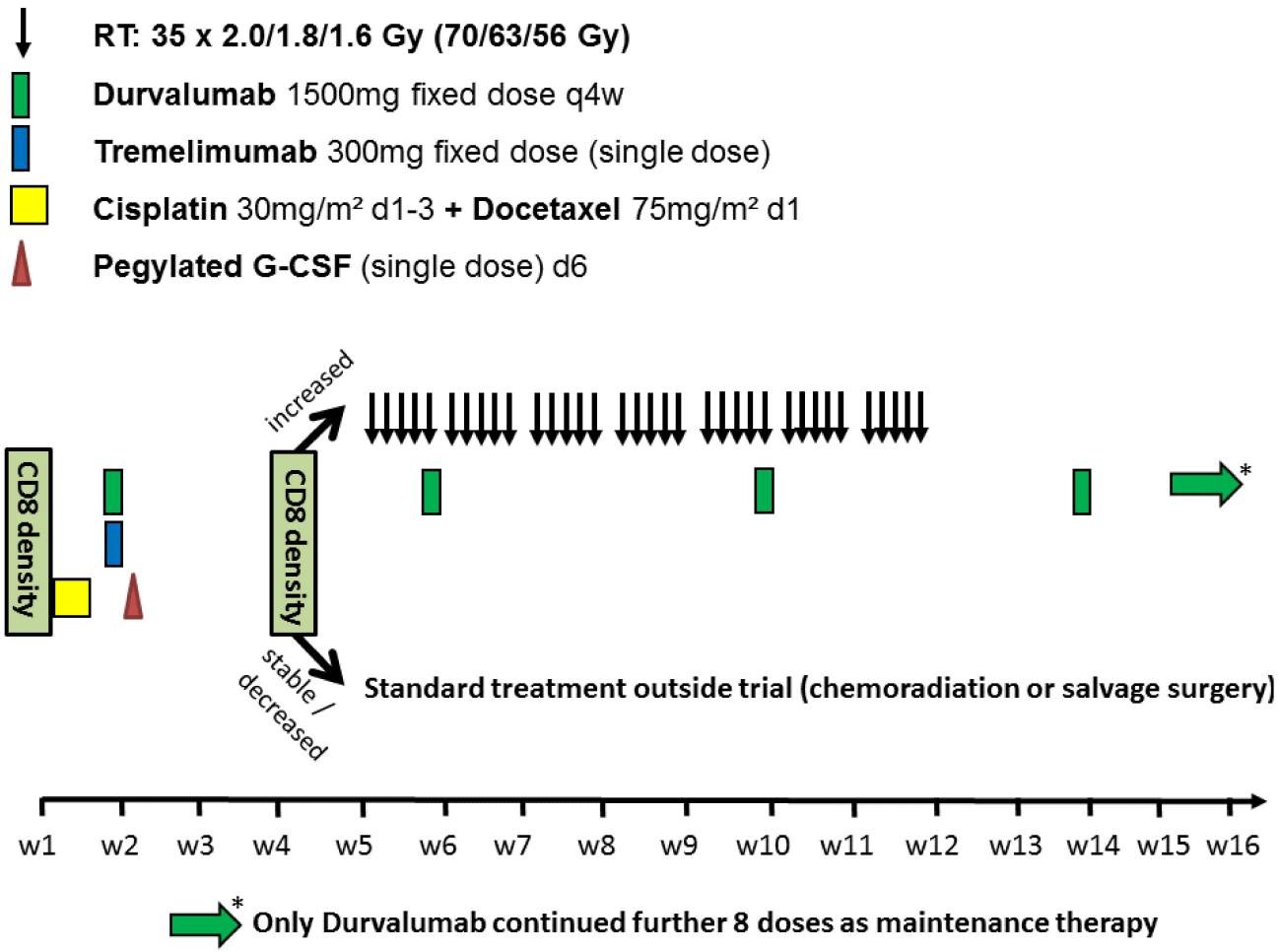


Clinical Study Protocol

Drug Substance Durvalumab (MEDI4736), Tremelimumab, Docetaxel, Cisplatin, Carboplatin

Study Code ESR-16-12356; Edition Number Version 1.5; Date 01.12.2020

Figure 2. B: Treatment flow chart "Expansion Cohort 1" (n=20)

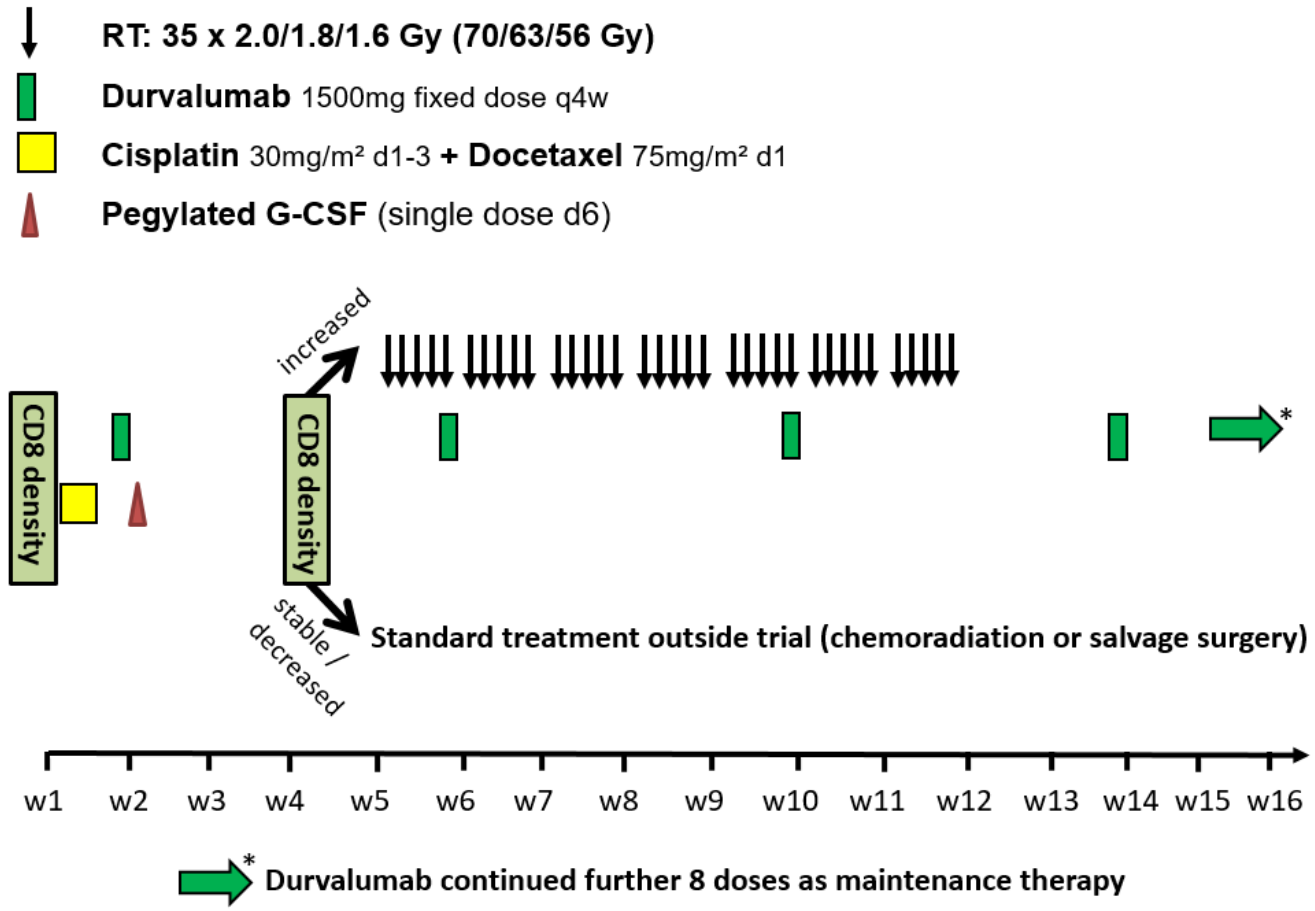


Clinical Study Protocol

Drug Substance Durvalumab (MEDI4736), Tremelimumab, Docetaxel, Cisplatin, Carboplatin

Study Code ESR-16-12356; Edition Number Version 1.5; Date 01.12.2020

Figure 2. C: Treatment flow chart "Expansion Cohort 2" (n=20)



3.3 Study oversight for safety evaluation

The study may be stopped if the principal investigator comes to the conclusion that patients are placed at undue risk because of clinically significant findings that meet any of the following criteria:

- Meet individual stopping criteria or are otherwise significant
- Are assessed as causally related to one of the study drugs or the combination of the drugs with radiotherapy
- Are not considered to be consistent with continuation of the study

Furthermore, the study may be stopped after the interim analysis, if the toxicity is inadequately high.

4. PATIENT SELECTION, ENROLLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Each patient must meet all of the inclusion criteria (Section 4.1) and none of the exclusion criteria (Section 4.2) for this study. Under no circumstances will there be exceptions to this rule.

4.1 Inclusion criteria

For inclusion in the study, patients should fulfill the following criteria:

- Written informed consent and any locally-required authorization (eg, HIPAA in the USA, EU Data Privacy Directive in the EU) obtained from the subject prior to performing any protocol-related procedures, including screening evaluations
- Age $\geq$ 18 years at time of study entry
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Locally advanced HNSCC, UICC stage III-IVB (oral cavity, oropharynx, hypopharynx, supraglottic larynx) (according to TNM version 8)
- Histological confirmation of HNSCC (regardless if p16 positive or negative)
- Measureable CD8 density in provided achival tumor tissue
- Body weight >30kg

- Adequate normal organ and marrow function as defined: Haemoglobin ≥ 9.0 g/dL; White Blood Cells (WBC) ≥ 3,000 per mm^3; Platelet count ≥100,000 per mm^3
- Serum bilirubin ≤ 1.5 x institutional upper limit of normal (ULN). This will not apply to subjects with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of hemolysis or hepatic pathology), who will be allowed only in consultation with their physician.
- AST (SGOT)/ALT (SGPT) ≤ 2.5 x institutional upper limit of normal (ULN)
- Creatinine Clearance >40ml/min (calculated from serum creatinine using the Cockcroft-Gault formula)
- Female subject of childbearing potential should have a negative serum pregnancy within 72 hours prior to receiving the first dose of durvalumab and tremelimumab A highly sensitive pregnancy test must be used.
- Female subjects of childbearing potential (must be willing to use a highly effective contraceptive measure as defined in the Clinical Trial Facilitation Group (CTFG) guideline ("Recommendations related to contraception and pregnancy testing in clinical trials.") For details see Section 7.1.1 of the study protocol. Highly effective contraception is required from screening to 90 days after the last dose of durvalumab monotherapy or 180 days after the last dose of durvalumab + tremelimumab combination therapy. (Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.)
- Male subjects of childbearing potential must agree to use a highly effective method of contraception as outlined in Section 7.1.1. Contraception, starting from screening to 90 days after the last dose of durvalumab monotherapy or 180 days after the last dose of durvalumab + tremelimumab combination therapy. (Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.)
- Subject 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.

4.2 Exclusion criteria

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

- Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)
- Participation in another clinical study with an investigational product during the last 4 weeks
- Concurrent enrolment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study
- Distant metastases
- Prior systemic anti-cancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumour embolization, monoclonal antibodies) of the locally advanced HNSCC
- Any other concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment, except the induction chemotherapy in the protocol. Concurrent use of hormonal therapy for non-cancer-related conditions (eg, hormone replacement therapy) is acceptable
- Prior radiotherapy of HNSCC
- Radiotherapy to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of study drug
- Major surgical procedure of the current locally advanced HNSCC (as defined by the Investigator). Note: Local surgery of isolated lesions for palliative intent is acceptable.
- History of allogenic organ transplantation.
- Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). The following are exceptions to this criterion:
    - Patients with vitiligo or alopecia areata
    - Patients with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement

  - Any chronic skin condition that does not require systemic therapy
  - Patients without active disease in the last 5 years may be included but only after consultation with the study physician
  - Patients with celiac disease controlled by diet alone

- Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent
- History of another primary malignancy except for
  - Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of IP and of low potential risk for recurrence
  - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
  - Adequately treated carcinoma in situ without evidence of disease
- History of active primary immunodeficiency
- Active infection including **tuberculosis** (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), **hepatitis B** (known positive HBV surface antigen (HBsAg) result), **hepatitis C**, or **human immunodeficiency virus** (positive HIV 1/2 antibodies). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
- Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab or tremelimumab. The following are exceptions to this criterion:
  - Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra articular injection)
  - Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent
  - Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication)

- Receipt of live attenuated vaccine within 30 days prior to the first dose of IP. Note: Patients, if enrolled, should not receive live vaccine whilst receiving IP and up to 30 days after the last dose of IP.
- Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of durvalumab monotherapy or 180 days after the last dose of durvalumab + tremelimumab combination therapy. This also applies to patients who receive only induction chemotherapy before the restaging endoscopy with biopsy.
- Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients.
- Prior randomisation or treatment in a previous durvalumab and/or tremelimumab clinical study regardless of treatment arm assignment.
- Past medical history of ILD, drug-induced ILD, radiation pneumonitis which required steroid treatment, or any evidence of clinically active interstitial lung disease.
- Known active bleeding diathesis.
- Judgment by the investigator that the patient is unsuitable to participate in the study and the patient is unlikely to comply with study procedures, restrictions and requirements.
- Known allergy or hypersensitivity to durvalumab, tremelimumab, cisplatin/carboplatin, docetaxel or any excipient
- Cisplatin/carboplatin induced polyneuropathy or hearing disorder

Procedures for withdrawal of incorrectly enrolled patients are presented in Section 4.3

If a patient withdraws from participation in the study, then his or her enrollment/randomization code cannot be reused. Withdrawn patients will not be replaced.

4.3 Withdrawal of subjects from study treatment and/or study

Permanent discontinuation of study treatment

An individual subject will not receive any further investigational product if any of the following occur in the subject in question:

1. An individual patient will not receive any further durvalumab + tremelimumab combination therapy or durvalumab monotherapy if their weight falls to 30kg or less

2. Withdrawal of consent or lost to follow-up

3. Adverse event that, in the opinion of the investigator or the sponsor, contraindicates further dosing

4. Subject is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing investigational therapy might constitute a safety risk

5. Pregnancy or intent to become pregnant

6. Dose-limiting toxicity (See Section 6.3.3 for definition of DLT)

7. Grade 3 infusion-related reaction that does not resolve within 6 hours with appropriate clinical management or any Grade 4 infusion-related reaction
8. Subject noncompliance that, in the opinion of the investigator or sponsor, warrants withdrawal; eg, refusal to adhere to scheduled visits

9. Initiation of alternative anticancer therapy including another investigational agent

10. Confirmation of PD and investigator determination that the subject is no longer benefiting from treatment with durvalumab + tremelimumab or durvalumab monotherapy. Subjects who are permanently discontinued from further receipt of investigational product, regardless of the reason (withdrawal of consent, due to an AE, other), will be identified as having permanently discontinued treatment

11. Subjects who are permanently discontinued from receiving investigational product will be followed for safety and tumor control, including the collection of any protocol-specified blood specimens, unless consent is withdrawn or the subject is lost to follow-up or enrolled I another clinical study. All subjects will be followed for survival. Subjects who decline to return to the site for evaluations will be offered follow-up by phone every 3 months as an alternative.

12. Study treatment is permanently discontinued if patients have progressive disease after induction chemo-immunotherapy or if their intratumoral CD8+ immune cells do no increase at least 20% compared to baseline.

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Withdrawal of consent

Patients are free to withdraw from the study at any time (IP and assessments) without prejudice to further treatment.

Patients who withdraw consent for further participation in the study will not receive any further IP or further study observation, with the exception of follow-up for survival, which will continue until the end of the study unless the patient has expressly withdrawn their consent to survival follow-up. E.g. subjects who discontinue treatment prior to completion of the treatment regimen should be strongly encouraged to participate in the safety follow up.

A patient who withdraws consent will always be asked about the reason(s) for withdrawal and the presence of any AE. The Investigator will follow up AEs outside of the clinical study.

If a patient withdraws consent, they will be specifically asked if they are withdrawing consent to:

- all further participation in the study including any further follow up (eg, survival contact telephone calls)
- withdrawal of consent to the use of their study generated data
- withdrawal to the use of any samples

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4.4 Replacement of subjects

If subjects are withdrawn from the study they will not be replaced.

5. INVESTIGATIONAL PRODUCT(S)

5.1 Durvalumab and tremelimumab

The Investigational Products Supply section of AstraZeneca/MedImmune will supply durvalumab and tremelimumab to the investigator as solutions for infusion after dilution.

5.1.1 Formulation/packaging/storage

Durvalumab (MEDI4736)

Durvalumab (MEDI4736) will be supplied by AstraZeneca as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab (MEDI4736), 26 mM histidine/histidine-hydrochloride, 275 mM trehalose dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 6.0. The nominal fill volume is 10.0 mL. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen.

Tremelimumab

Tremelimumab will be supplied by AstraZeneca as a 400-mg vial solution or 25-mg vial solution for infusion after dilution. The solution contains 20 mg/mL tremelimumab, 20 mM histidine/histidine hydrochloride, 222 mM trehalose dihydrate, 0.27 mM disodium edetate dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 5.5. The nominal fill volume is either 20.0 mL or 1.25 mL . Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen.

5.2 Dose and treatment regimens

5.2.1 Treatment regimens

Durvalumab + tremelimumab combination therapy

Patients in the ”Main Cohort” will receive durvalumab (MEDI4736) (1500mg Q4W) in combination with tremelimumab (75 mg IV Q4W) for up to 4 doses/cycles, followed by durvalumab (MEDI4736) 1500mg Q4W for up to a maximum of 8 additional doses/cycles unless there is confirmed disease progression, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. The first durvalumab (MEDI4736) monotherapy dose at 1500mg Q4W will be 4 weeks after the final dose of durvalumab (MEDI4736) in combination with tremelimumab.

Patients in the ”Expansion Cohort 1” will receive durvalumab (MEDI4736) (1500mg Q4W) in combination with tremelimumab (300 mg IV single dose), followed by durvalumab (MEDI4736) 1500mg Q4W for up to a maximum of 11 additional doses/cycles unless there is confirmed disease progression, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. The first durvalumab (MEDI4736) monotherapy dose at 1500mg Q4W will be 4 weeks after the dose of durvalumab (MEDI4736) in combination with tremelimumab.

Tremelimumab will be administered first; the durvalumab (MEDI4736) infusion will start approximately 1 hour (maximum 2 hours) after the end of the tremelimumab infusion. If there are no clinically significant concerns after the first cycle, then, at the discretion of the Investigator, all other cycles of durvalumab (MEDI4736) can be given immediately after the tremelimumab infusion has finished.

Patients in the “Expansion Cohort 2” will receive durvalumab (MEDI4736) (1500mg Q4W) in monotherapy for up to 12 doses/cycles unless there is confirmed disease progression, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

5.2.2 Duration of treatment and criteria for retreatment

All treatment will be administered beginning on Day 1 for up to 12 months ("Main cohort": 4 cycles of durvalumab (MEDI4736) + tremelimumab combination therapy followed by 8 cycles of durvalumab (MEDI4736) monotherapy; "Expansion Cohort 1": 1 cycles of durvalumab (MEDI4736) + tremelimumab combination therapy followed by 11 cycles of durvalumab (MEDI4736) monotherapy; "Expansion Cohort 2": 12 cycles of durvalumab (MEDI4736) monotherapy) unless there is confirmed PD, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

Patients with CR after radioimmunotherapy (confirmed in Restaging 2, which is performed after treatment cycle 6) will continue with further 6 cycles of durvalumab. Patients with PR/SD after radioimmunotherapy that receive complete tumor resection will also continue with further 6 cycles of durvalumab.

Patients with rapid tumor progression or with symptomatic progression that requires urgent medical intervention (e.g., central nervous system metastasis, respiratory failure due to tumor compression, spinal cord compression) will not be eligible for continuing durvalumab (MEDI4736) ± tremelimumab.

No retreatment is planned.

Patients who AstraZeneca and the Investigator determine may not continue treatment after PD will be followed up for survival. Patients who have discontinued treatment due to toxicity or symptomatic deterioration, or who have commenced subsequent anticancer therapy, will be followed up until confirmed disease progression and for survival.

5.2.3 Study drug preparation of durvalumab and tremelimumab

Based on average body WT of 75 kg, 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) and

- "Main Cohort": 75 mg Q4W tremelimumab (equivalent to 1 mg/kg Q4W)
  OR
- "Expansion Cohort 1": 300 mg tremelimumab (equivalent to 4 mg/kg single cycle)

is included in the current study.

Preparation of durvalumab doses for administration with an IV bag

Total time from needle puncture of the durvalumab (MEDI4736) vial to the start of administration should not exceed:

- 24 hours at 2°C to 8°C (36°F to 46°F)
- 4 hours at room temperature

A dose of 1500mg (for patients >30kg in weight) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab (MEDI4736) concentration ranging from 1 to 20 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter. Add 30.0 mL of durvalumab (MEDI4736) (i.e., 1500mg of durvalumab [MEDI4736]) to the IV bag. The IV bag size should be selected such that the final concentration is within 1 to 20 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

Standard infusion time is 1 hour. However, if there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature.

Do not co-administer other drugs through the same infusion line.

In the event that either preparation time or infusion time exceeds the time limits a new dose must be prepared from new vials. Durvalumab (MEDI4736) does not contain preservatives, and any unused portion must be discarded.

No incompatibilities between durvalumab and polyvinylchloride or polyolefin IV bags have been observed.

Preparation of tremelimumab doses for administration with an IV bag

Total time from needle puncture of the tremelimumab vial to the start of administration should not exceed:

- 24 hours at 2°C to 8°C (36°F to 46°F)
- 4 hours at room temperature

A dose of 75 mg will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final tremelimumab concentration ranging from 0.10 to 10 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter. Add 3.8 mL (ie,75 mg of tremelimumab, with the dose volume rounded to the nearest tenth mL) to the IV bag. The IV bag size should be selected such that the final concentration is within 0.10 to 10 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag. Standard

infusion time is 1 hour. However, if there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature.

Do not co-administer other drugs through the same infusion line.

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

No incompatibilities between tremelimumab and polyvinylchloride or polyolefin have been observed.

5.2.4 Monitoring of dose administration

Patients will be monitored during and after the infusion with assessment of vital signs at the times specified in the Study Protocol.

In the event of a ≤Grade 2 infusion-related reaction, the infusion rate of study drug may be decreased by 50% or interrupted until resolution of the event and re-initiated at 50% of the initial rate until completion of the infusion. For patients with a ≤Grade 2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen and/or an antihistamine (e.g., diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator. If the infusion-related reaction is ≥Grade 3 or higher in severity, study drug will be discontinued. For management of patients who experience an infusion reaction, please refer to the toxicity and management guidelines in appendix 1.

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

5.2.5 Accountability and dispensation

The investigator or an authorized person is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the centers or the subjects and the amount remaining at the conclusion of the trial. For all trial sites, the Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate.

5.2.6 Disposition of unused investigational study drug

The site will account for all investigational study drug dispensed and also for appropriate destruction. Certificates of delivery and destruction must be signed.

5.3 Additional study drugs

Additional chemotherapy is used in the induction phase of the trial. All the used drugs docetaxel in combination with cisplatin or carboplatin are approved and frequently used in clinical routine. If possible patients will receive the combination of docetaxel and cisplatin. Patients with creatinine clearance <60ml/min or impaired cardiac output not appropriate for sufficient hydration will receive the combination of carboplatin and docetaxel.

5.3.1 Docetaxel

Docetaxel is generally available and a routine treatment schedule for locally advanced HNSCC. Thus, it will be prescribed by the treating physician and not provided by the Sponsor or a third party. Thus, there are no requirements to maintain trial-specific records of the inventory at the sites, the use of each subject, and the delivery, storage and destruction (i.e. no measures of drug accountability beyond the general routine practice in the respective institutions). By filling in the CRF, the investigators or designees adequately document that subjects were provided the doses specified in the protocol.

5.3.1.1 Formulation/packaging/storage

Docetaxel is available as 10mg/ml or 20mg/ml concentrate from different manufacturers and can be stored at room temperature.

5.3.1.2 Doses and treatment regimens

Subjects will be administered docetaxel in line with normal clinical practice, with a dose and schedule of 75mg/m²/d body surface area (BSA) on day 1. For a BSA above 2.0m² the dose will be capped at the one calculated for 2.0m² BSA.

One cycle will be administered in every subject.

5.3.1.3 Product preparation

The required volume of docetaxel is added to 250ml of glucose 5% or sodium chloride 0.9%.

5.3.1.4 Dose administration

The recommended premedication before the administration in combination with cisplatin or carboplatin is dexamethasone 8mg, ondansetrone 8mg, clemastine 2mg and ranitidine 50mg. Prophylactic G-CSF is recommended (after Amendment 3, protocol version 1.4, 08.01.2020).

5.3.1.5 Monitoring of dose administration

Dose administration should be performed under supervision of an experienced oncologist or radiation oncologist and follow standard procedures of the treatment site.

5.3.2 Cisplatin

Cisplatin is generally available and a routine treatment schedule for locally advanced HNSCC. Thus, it will be prescribed by the treating physician and not provided by the Sponsor or a third party. Thus, there are no requirements to maintain trial-specific records of the inventory at the sites, the use of each subject, and the delivery, storage and destruction (i.e. no measures of drug accountability beyond the general routine practice in the respective institutions). By filling in the CRF, the investigators or designees adequately document that subjects were provided the doses specified in the protocol.

5.3.2.1 Formulation/packaging/storage

Cisplatin is available as 0,5mg/ml or 1mg/ml concentrate from different manufacturers and can be stored at room temperature.

5.3.2.2 Doses and treatment regimens

Subjects will be administered cisplatin in line with normal clinical practice, with a dose and schedule of 30mg/m²/d body surface area (BSA) on day 1-3. For a BSA above 2.0m² the dose will be capped at the one calculated for 2.0m² BSA. One cycle will be administered in every subject.

5.3.2.3 Product preparation

The required volume of cisplatin is added to sodium chloride 0.9% alone or in combination with glucose 5% or mannitol 1,875%.

5.3.2.4 Dose administration

The recommended premedication before the administration is dexamethasone 8mg and ondansetrone 8mg. An adequate hydration is required before and after drug administration. Prophylactic G-CSF is recommended (after Amendment 3, protocol version 1.4, 08.01.2020).

5.3.2.5 Monitoring of dose administration

Dose administration should be performed under supervision of an experienced oncologist or radiation oncologist and follow standard procedures of the treatment site.

5.3.3 Carboplatin

Carboplatin is generally available and a routine treatment schedule for locally advanced HNSCC. Thus, it will be prescribed by the treating physician and not provided by the Sponsor

or a third party. Thus, there are no requirements to maintain trial-specific records of the inventory at the sites, the use of each subject, and the delivery, storage and destruction (i.e. no measures of drug accountability beyond the general routine practice in the respective institutions). By filling in the CRF, the investigators or designees adequately document that subjects were provided the doses specified in the protocol.

5.3.3.1 Formulation/packaging/storage

Carboplatin is available as 10mgmg/ml concentrate from different manufacturers and can be stored at room temperature.

5.3.3.2 Doses and treatment regimens

Subjects will be administered carboplatin in line with normal clinical practice, with a dose and schedule of AUC 1.5 on day 1-3. One cycle will be administered in every subject.

5.3.3.3 Product preparation

The required volume of carboplatin is added to glucose 5% or sodium chloride 0.9%.

5.3.3.4 Dose administration

The recommended premedication before the administration is dexamethasone 8mg and ondansetrone 8mg. Prophylactic G-CSF is recommended (after Amendment 3, protocol version 1.4, 08.01.2020).

5.3.3.5 Monitoring of dose administration

Dose administration should be performed under supervision of an experienced oncologist or radiation oncologist and follow standard procedures of the treatment site.

5.3.4 Definition of DLT

Dose-limiting toxicities (DLTs) will be evaluated during the whole trial. The period for evaluating DLTs will be from the time of first to the last administration of durvalumab or tremelimumab. Grading of DLTs will follow the guidelines provided in the Common Terminology Criteria for Adverse Events (CTCAE) version.

A DLT will be defined as any Grade 3 or higher toxicity that occurs during the trial and is attributable to immunotherapy. Toxicity that is clearly and directly related to the primary disease or to another etiology is excluded from this definition. Especially typical radiotherapy induced grade 3 toxicities will be excluded, as they happen frequently during standard CRT. The following will be DLTs:

- Any Grade 4 irAE
- Any ⩾ Grade 3 colitis
- Any Grade 3 or 4 noninfectious pneumonitis irrespective of duration
- Any Grade 2 pneumonitis that does not resolve to ⩽ Grade 1 within 3 days of the initiation of maximal supportive care
- Any Grade 3 irAE, excluding colitis or pneumonitis, that does not downgrade to Grade 2 within 3 days after onset of the event despite optimal medical management including systemic corticosteroids or does not downgrade to ⩽ Grade 1 or baseline within 14 days
- Liver transaminase elevation > 8 × ULN or total bilirubin > 5 × ULN
- Any ⩾ Grade 3 non-irAE, except for the exclusions listed below
- Any cases meeting the definition of Hy's law (AST and/or ALT ≥3 × ULN together with total bilirubin >2 × ULN without initial findings of cholestasis (ie, elevated alkaline phosphatase) and absence of any alternative cause)
- Any ⩾ Grade 3 infusion reaction caused by durvalumab or tremelimumab infusion

The definition excludes the following conditions:

- Grade 3 fatigue lasting ⩽ 7 days
- Grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency) that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the subject is asymptomatic
- Grade 3 inflammatory reaction attributed to a local antitumor response (eg, inflammatory reaction at sites of metastatic disease, lymph nodes, etc)
- Concurrent vitiligo or alopecia of any AE grade
- Grade 3 or 4 neutropenia that is not associated with fever or systemic infection that improves by at least 1 grade within 3 days. Grade 3 or Grade 4 febrile neutropenia will be a DLT regardless of duration or reversibility
- Grade 3 or 4 lymphopenia
- Grade 3 thrombocytopenia that is not associated with clinically significant bleeding that requires medical intervention, and improves by at least 1 grade within 3 days
- Isolated Grade 3 electrolyte abnormalities that are not associated with clinical signs or symptoms and are reversed with appropriate maximal medical intervention within 3 days

The following radiation induced toxicities will be excluded:

- Grade 3 Radiation dermatitis
- Grade 3 Mucositis
- Grade 3 Dysphagia

- Grade 3 Xerostomia
- Other local Grade 3 AEs, that are clearly attributable to radiotherapy

Immune-related AEs are defined as AEs of an immune nature (i.e., inflammatory) in the absence of a clear alternative etiology. In the absence of a clinically significant abnormality, repeat laboratory testing will be conducted to confirm significant laboratory findings prior to designation as a DLT.

In case of a DLT the treatment with durvalumab and tremelimumab will be stopped immediately. If the DLT occurs during radiotherapy, Durvalumab and Tremelimumab will be stopped, but the radiotherapy will be continued as scheduled. If the DLT occurs before the beginning of the radiotherapy Durvalumab and Tremelimumab is stopped and a concomitant chemotherapy may be administered during radiotherapy after discussion with the principal investigator.

A descriptive analysis of (serious) adverse events is performed after 20 patients have a complete documentation until the end of their radiotherapy period. This interim analysis may allow for early termination of the trial in case of unexpected toxicities or unexpectedly high frequencies of severe AEs.

5.4 Radiotherapy

A standard radiotherapy for locally advanced HNSCC will be performed in curative intention. Technical requirements, target volumes and fractionation are described in the treatment plan (section 6.4).

6. TREATMENT PLAN

6.1 Subject enrollment

6.1.1 Trial design

The trial is a single arm open-label study. Thus, there is no randomization and no blinding. Both investigators and patients know the treatment scheme.

6.1.2 Procedures for handling subjects incorrectly enrolled

Subjects that are incorrectly enrolled but are not yet initiated on treatment will be withdrawn from the study.

6.2 Pathologic assessment of CD8 density

The initial formalin-embedded biopsy taken from the patient during pan-endoscopy prior treatment must be sent during the screening phase to the reference pathology: Department of Pathology of the University Hospitals Erlangen. Detailed specifications about procedures and quality assurance are given in section 8.3.1. CD8+ tumor infiltrating immune cells will be stained following a standard procedure using an automated stainer. The density of CD8+ tumor infiltrating immune cells will be analyzed quantitatively. After induction chemo-immunotherapy a second endoscopy with biopsy will be performed. The density of tumor infiltrating CD8+ immune cells of this second biopsy will be compared to the first biopsy. An increase of at least 20% will be scored as significant increase. Samples with an increase below 20% will be scored as stable. Two independent experienced pathologists will evaluate the CD8 density. Patients with increased CD8 density or pCR of their primary tumor will continue with durvalumab + tremelimumab and enter radioimmunotherapy. Patients with stable or decreased CD8 density or progressive disease will stop durvalumab + tremelimumab and receive a standard CRT outside the trial.

If a salvage resection is required, the surgical specimen should also be sent to the reference pathology to assess the CD8 density in the residual tumor tissue as part of the translational program.

6.3 Dosage and administration of drugs

6.3.1 Induction chemotherapy

As described in section 5.3 additional chemotherapy is used in the induction phase of the trial. All the used drugs docetaxel in combination with cisplatin or carboplatin are approved and frequently used in clinical routine. If possible, patients will receive the combination of docetaxel and cisplatin. A docetaxel dose of 75mg/m²/d body surface area (BSA) will be used and administered on day 1. Cisplatin will be administered in a dose of 30mg/m²/d BSA from day 1-3. For a BSA above 2.0m² the dose will be capped at the one calculated for 2.0m² BSA. An adequate hydration is required before and after administration of cisplatin. Patients with creatinine clearance <60ml/min or impaired cardiac output not appropriate for sufficient hydration will receive carboplatin instead of cisplatin. Patients will receive carboplatin AUC 1.5 per day on day 1-3. The recommended premedication before the administration of docetaxel in combination with cisplatin or carboplatin (day 1) is dexamethasone 8mg, ondansetrone 8mg, clemastine 2mg and ranitidine 50mg. Before the administration of cisplatin or carboplatin (day 2-3) a premedication with dexamethasone 8mg and ondansetrone 8mg is recommended. A chemotherapy infusion plan including recommended premedication is provided by the leading

center. Prophylactic administration of G-CSF is recommended (after Amendment 3, protocol version 1.4, 08.01.2020).

6.3.2 Durvalumab + Tremelimumab and durvalumab maintenance

Patients in the "Main Cohort" will start treatment with one cycle of induction chemotherapy (day 1-3) and durvalumab + tremelimumab (day 5). If patients enter radioimmunotherapy the next two durvalumab + tremelimumab administrations will be concomitant to radiotherapy (day 33 and 61). The last durvalumab + tremelimumab administration will be after completion of radiotherapy (day 89). This treatment scheme will be followed by two further administration of durvalumab Q4W. In case of CR in the restaging or PD/SD followed by complete surgical tumor resection, durvalumab will be continued for further six cycles Q4W as maintenance therapy.

On the day of immunotherapy tremelimumab is always administered before durvalumab. Tremelimumab will be administered in a fixed dose of 75mg Q4W. Afterwards durvalumab is administered in a fixed dose of 1500mg Q4W.

In the "Expansion Cohort 1" Tremelimumab administration will be limited to a single dose of 300mg on day 5. Further treatment will be performed with durvalumab monotherapy.

In the "Expansion Cohort 2" patients will be treated with durvalumab monotherapy (without tremelimumab).

6.3.3 Dose modification and toxicity management

6.3.3.1 Toxicity management of durvalumab + tremelimumab

The following general guidance should be followed for management of toxicities.

- Treat each of the toxicities with maximum supportive care (including holding the agent suspected of causing the toxicity if required).
- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of the assigned IP along with appropriate continuing supportive care
- Dose modifications are not allowed.

All toxicities will be graded according to NCI CTCAE, Version 4.03.

Guidelines for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions for durvalumab monotherapy and durvalumab + tremelimumab are provided in the Dosing Modification and Toxicity Management Guidelines in appendix 1.

In addition, there are certain circumstances in which durvalumab and tremelimumab should be permanently discontinued (see the Dosing Modification and Toxicity Management Guidelines in appendix 1.

Following the first dose of IP, subsequent administration of durvalumab and tremelimumab can be modified based on toxicities observed as described in the Dosing Modification and Toxicity Management Guidelines. These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to durvalumab monotherapy and the durvalumab + tremelimumab regimen by the reporting investigator.

Dose reductions are not permitted. In case of doubt, the Investigator should consult with the Study Physician.

6.3.3.2 Toxicity management of Radiotherapy

Radiotherapy frequently induces radiation dermatitis, mucositis and dysphagia. The implantation of a percutaneous endoscopic gastrostomy feeding tube prior radiotherapy is recommended to ensure sufficient nutrition. Mouth rinse should be provided either prophylactically or at least at onset of mucositis. As oral thrush frequently appears after radiation mucositis, local anti-mycotic treatment is recommended. Unguents should be used after onset of radiation dermatitis. In case of bacterial superinfection antibiotics should be considered. Analgesic treatment should be started depending on the patient's complaints

6.4 Radiotherapy

6.4.1 Technical requirements

Megavolt equipment of 6 MeV or 12 MeV is essential. A multi-leaf collimator is necessary to allow customized blocking and intensity modulation. Intensity modulated radiation therapy (IMRT) will be performed with linear accelerators or tomotherapy. Both static and dynamic delivery of radiation is possible. The boost will be administered as simultaneous integrated boost (SIB). In order to ensure adequate radiation delivery, image guided radiation therapy is essential.

6.4.2 Subject positioning and imaging

All patients are irradiated in supine position. Individually customized treatment masks will be used for immobilization. This allows an exact inter- and intrafractional positioning. A radiotherapy planning CT will be performed in the customized mask. A CT slice thickness of not more than 3 mm is recommended. For an appropriate image quality the use of i.v. contrast in the planning CT scan is required. If no i.v. contrast can be used, image fusion with a contrast enhanced diagnostic CT or MRI is mandatory.

6.4.3 Target volume definition

Target volumes will be defined according to ICRU reports #50, #62 and #83.

6.4.3.1 Gross Tumor Volume (GTV)

The GTV is defined as the primary tumor volume and involved cervical lymph nodes. Lymph nodes are considered to be involved if they are >1cm in the short axis (axial images). Smaller nodes with central necrosis or extracapsular extension (ECE) are also considered to be involved. The GTV has to be contoured separately on the initial CT or MRT before the induction chemo-immunotherapy (GTVpre) and after the induction (GTVpost). The GTV is the union of GTVprae and GTVpost. As mentioned above at least one contrast enhanced CT (either diagnostic or planning CT) or MRI is required for GTV delineation. If a FDG-PET/CT was performed additional FDG enhanced lymph nodes should be included in the GTV.

6.4.3.2 Clinical Target Volumes (CTV)

Clinical target volume 1 (CTV1):

The CTV1 consists of the GTV of the primary tumor and the involved lymph nodes before and after induction chemo-immunotherapy. An additional safety margin of 5-10mm should be added. Regions with anatomic or physical barriers (air, bone, etc.) should be excluded.

Clinical target volume 2 (CTV2):

CTV2 includes CTV1. Furthermore, the whole neck levels with involved lymph nodes should be included. The medial supraclavicular fossa should not be included in CTV2 due to the brachial plexus.

Clinical target volume 3 (CTV3):

The CTV3 includes the CTV2 and nodal levels with risk of microscopic tumor involvement. The neck node levels will be contoured according to the guidelines defined by a consensus panel[100]. The recommendation for lymph node levels to include in CTV3 is shown in Table 1.

An unilateral neck treatment may be considered in case of tumors of retromolar trigonum or tonsil at least 1cm distant from the midline with ipsilateral N1-N2a neck.

Table 1: **Recommendation for lymph node levels to be included in CTV3**

Nodal stage	**Ipsilateral neck levels to be involved**							
	Level Ia	Level Ib	Level II	Level III	Level IV	Level V	Level VI	Level VIIa (RP)
N0-N1			X	X	X			
N2a-N2b		X	X	X	X	X		X
N2c		X	X	X	X	X		X
N3	X	X	X	X	X	X		X
	Contralateral neck levels to be involved							
	Level Ia	Level Ib	Level II	Level III	Level IV	Level V	Level VI	
N0-N1			X	X	X			
N2a-N2b			X	X	X			
N2c	Depending on N stage of contralateral neck							
N3	Depending on N stage of contralateral neck							

Additional notes:

- Include level Ia for anterior tongue and base of the mouth
- Includel level Ib also if N0 for all oral cavity tumors and others with extension to the oral cavity
- Include level Ib in case of level II involvement
- Include level VI in case of extension to glottis, piriform sinus or esophagus
- Include level VIIa (RP; retropharyngeal nodes) for all primary tumor crossing the midline or involving the posterior pharyngeal wall (ipsilateral and contralateral)
- Include level VIIb (retrostyloid nodes) in case of involved level II nodes
- Include medial supraclavicular fossa in case of involved level IV nodes
- Include the whole sternocleidomastoid muscle in case of tumor infiltration

6.4.3.3 Planning Target Volumes (PTV)

PTV1, PTV2 and PTV3 will enclose CTV1, CTV2 and CTV3. As usual, radiation dose will be prescribed to these PTVs as they account for day to day set up and patient movement. For the PTV an additional safety margin of 3-5mm is recommended depending on the set up and imaging of the treating center.

6.4.4 Dose prescription and dose specification of radiotherapy

Dose prescription, specification and reporting will be performed as recommended in the ICRU 83 report. Subjects will be treated with intensity modulated radiotherapy (IMRT) with simultaneous integrated boost (SIB). Five fractions will be delivered per week. Radiotherapy

should start always on Monday and only in case of logistical reasons on Tuesday. Altogether 35 fractions of radiotherapy will be delivered. The single fraction doses in PTV1 / PTV2 / PTV3 will be 2.0 / 1.8 / 1.6Gy. The resulting cumulative dose in PTV1 / PTV2 / PTV3 will be 70.0 / 63.0 / 56.0 Gy.

6.4.5 Organs at risk

Organs at risk must be delineated and considered in the treatment planning. The following dose-volume parameters are recommended.

Table 2: Organs at risk

Dose limits for critical normal structures (adapted from Wannemacher et al[101] and Hristow et al[102] that base on RTOG guidelines). Dose limits were approved by the DEGRO Expertenkommission (24.10.2017).

	Maximum dose (Dmax)	Mean dose (Dmean)
brainstem	≤ 54 Gy	
Spinal cord	≤ 45 Gy	
Ipsilateral parotid		as low as possible
Contralateral parotid		≤ 25 Gy (if possible)
Lips		≤ 30Gy (if possible)
Mandibula	≤ 70 Gy	
Cochlea	≤ 40 Gy	

6.4.6 Treatment verification

Routine imaging has to be performed in all patients at least once weekly. Image guidance with KV/MV images or accelerator mounted cone-beam CT is possible. The bony anatomy will be matched. Due to a possible tumor shrinkage or neck edema it is recommended to repeat the planning CT scan after the delivery of 20 fractions if no cone-beam CTs are performed. In case of relevant anatomic changes of the patient's neck a re-planning is necessary.

6.4.7 Treatment interruption or preliminary end of radiotherapy

Treatment interruptions should be avoided unless there is no other medical possibility. It is possible to compensate for missed treatments with a twice daily treatment delivery. A

preliminary abortion of radiotherapy should be avoided. In case of the medical need to stop radiotherapy before the complete dose has been delivered, the principal investigator must be informed immediately.

6.5 Surgery

At week 12 after radiotherapy imaging of the neck will be performed with contrast enhanced CT and/or MRI. An FDG-PET/CT is optional. If there is residual persistent disease in the neck, a neck dissection is recommended[103]. The extent of the neck dissection is at the discretion of the treating head and neck surgeon. In case of a suspicious local lesion, a pan-endoscopy with biopsy should be performed. In case of a positive biopsy, a salvage intervention is recommended. Salvage surgery should be planned at the discretion of the treating head and neck surgeon, if the patient is fit for the planned intervention and accepts the intervention and its potential side effects. The time period from the last durvalumab administration should be at least one week. After surgery durvalumab maintenance should only be started when the wound healing is completed. In case of delayed wound healing durvalumab can be administered delayed up to 4 weeks (time period of one cycle), the following time intervals up to cycle 6 will be the usual q4w. In case of a longer delay, the principal investigator has to be contacted. Surgical specimens with residual tumor are to be submitted to the reference pathology at the university hospitals Erlangen.

7. RESTRICTIONS DURING THE STUDY AND CONCOMITANT TREATMENT(S)

7.1 Restrictions during the study

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

7.1.1 Contraception

For this trial, male subjects will be considered to be of non-reproductive potential if they are permanently sterile by bilateral orchidectomy.

Female subjects will be considered of non-reproductive potential if they are either:

- postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not

using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);
- have had a hysterectomy and/ or bilateral oophorectomy and/ or bilateral salpingectomy, at least 6 weeks prior to screening;

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, from screening to 90 days after the last dose of durvalumab monotherapy or 180 days after the last dose of durvalumab + tremelimumab combination therapy by complying with one of the following:

practice abstinence† from heterosexual activity;
OR
use (or have their partner use) highly effective contraception during heterosexual activity.

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/ IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

Methods of contraception for female participants with child bearing potential must be highly effective. The following methods are allowed for female participants in the trial:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
    - oral
    - intravaginal
    - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation:
    - oral
    - injectable
    - implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner (after medical assessment of surgical success)

For male participants in the trial with women with child bearing potential the following methods of contraception are allowed:
- highly effective method of contraception of the women with child bearing potential (see above)
- bilateral vasectomy (after medical assessment of surgical success)
- Condoms

Highly effective contraception is required from screening to 90 days after the last dose of durvalumab monotherapy or 180 days after the last dose of durvalumab + tremelimumab combination therapy. Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of initiation of study treatment (or 14 days prior to the initiation of study treatment for oral contraception) throughout the study period up to to 90 days after the last dose of durvalumab monotherapy or 180 days after the last dose of durvalumab + tremelimumab combination therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

7.1.2 Blood donationSubjects should not donate blood for at least 90 days following the last infusion of durvalumab or tremelimumab or 90 days after receipt of the final dose of durvalumab.

7.2 Concomitant treatment(s)

The Investigator must be informed as soon as possible about any excluded concomitant medication taken from the time of screening until the end of the clinical phase of the study (final study visit). Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the CRF.

Restricted, prohibited, and permitted concomitant medications are described in the following tables. Refer to Section 6.3.3 for guidance on management of IP-related toxicities.

7.2.1 Permitted concomitant medications

Table 3. **Supportive medications**

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

7.2.2 Excluded Concomitant Medications

Table 4. **Prohibited concomitant medications**

Prohibited medication/class of drug:	Usage:
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment. (Concurrent use of hormones for non-cancer-related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [eg, by local surgery or radiotherapy])

Prohibited medication/class of drug:	**Usage:**
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers	*Should not be given concomitantly, or used for premedication prior to the I-O infusions. The following are allowed exceptions:* • *Use of immunosuppressive medications for the management of IP-related AEs,* • *Glucocorticoids as premedication during the induction chemotherapy before the administration of docetaxel and cisplatin/carboplatin (before the first administration of durvalumab+tremelimumab)* • *Use in patients with contrast allergies.* • *In addition, use of inhaled, topical, and intranasal corticosteroids is permitted.* *A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of the patient (eg, chronic obstructive pulmonary disease, radiation, nausea dyspnea due to edema of the neck, etc).*
Drugs with laxative properties and herbal or natural remedies for constipation	Should be used with caution through to 90 days after the last dose of tremelimumab during the study
Sunitinib	Should not be given concomitantly or through 90 days after the last dose of tremelimumab (acute renal failure has been reported with combination therapy of tremelimumab and sunitinib)
EGFR TKIs	Should not be given concomitantly. Should be used with caution in the 90 days post last dose of durvalumab. Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with 1st generation EGFR TKIs) has been reported when durvalumab has been given concomitantly.
Live attenuated vaccines	Should not be given through 30 days after the last dose of IP (including SoC)
Herbal and natural remedies which may have immune-modulating effects	Should not be given concomitantly unless agreed by the sponsor

8. STUDY PROCEDURES

8.1 Schedule of study procedures

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

For all treatment arms

- Patient reported outcomes (PRO) and tumor efficacy (RECIST) assessment dates are not affected by dose delays and remain as originally scheduled, as they are based on the date of randomization (not the date of therapy).
- All other scheduled assessments must be performed relative to the start of the dosing cycle such that all laboratory procedures, etc. required for dosing should be performed within 3 days prior to dosing.

For durvalumab monotherapy or durvalumab + tremelimumab combination arms

- Patients may delay dosing under certain circumstances.
  - Dosing may be delayed per Toxicity Management Guidelines, due to either an immune or a non-immune-related AE.
  - If dosing must be delayed for reasons other than treatment-related toxicity, dosing will resume as soon as feasible
  - The second administration of durvalumab and tremelimumab has to be delayed for one week or two weeks if the beginning of radiotherapy has to be delayed for one week or two weeks if CD8 evaluation is not available on day 29. In case of longer delay, the principal investigator has to be contacted.
  - In case of a dose delay, the subsequent dosing intervals will not be shortened.

8.1.1 Pre-screening

Pre-screening procedures will be performed up to 42 days before day 1. All subjects must first read, understand, and sign the IRB/REB/IEC-approved ICF before any study-specific screening procedures are performed. After signing the ICF, completing all screening procedures and being deemed eligible for entry, subjects will be enrolled in the study. Procedures that are performed prior to the signing of the ICF and are considered standard of care may be used as screening assessments if they fall within the 28-day screening window. In the pre-screening a paraffin-embedded biopsy from every subject is to be sent to the reference pathology at the university hospitals Erlangen for assessment of CD8 density.

8.1.2 Screening Phase

Screening procedures will be performed up to 28 days before day 1.

The following procedures will be performed during the Screening Visit:

- Review of inclusion/exclusion criteria
- Medical history and demographics including smoking and alcohol
- ECOG Performance Status
- Review of concomitant medications
- Review baseline of adverse events
- Patient questionnaires
- Full physical exam
- Dental check-up
- Vitals signs, weight and height
- 12-lead ECG (in triplicate [2-5 minutes apart])
- Echocardiography
- Imaging:
  - Contrast enhanced CT / MRI neck
  - CT Thorax
  - Abdominal CT / Sonography
- Clinical laboratory tests for:
  - HIV and Hepatitis B/C serology
  - Coagulation (PT/INR, aPTT)
  - Serum Creatinine
  - Highly sensitive serum pregnancy test (for women of childbearing potential only)
  - Hematology
  - Urinalysis
  - Clinical chemistry
  - TSH

- Blood for correlative studies

8.1.3 Treatment Phase

Procedures to be conducted during the treatment phase of the study are presented in the Schedule of Assessments.

Before every administration of durvalumab + tremelimumab or durvalumab alone the following procedures will be performed:

- ECOG performance status
- Review of concomitant medications
- Review of adverse events
- Directed physical examination
- Vital signs and weight
- Clinical laboratory tests for:
  - Highly sensitive serum pregnancy test (for women of childbearing potential only)
  - Hematology
  - Clinical chemistry
  - TSH
  - Blood for correlative studies (except before first administration)

The laboratory tests (hematology, clinical chemistry, TSH) and the highly sensitive pregnancy test (women of child bearing potential only) need to be performed such that results are available and can be reviewed by the investigator prior to administration of durvalumab monotherapy or durvalumab + tremelimumab combination.

The NADIR of leucocytes and thrombocytes is expected two weeks after induction chemotherapy. Consequently, hematology and clinical chemistry has to be performed twice weekly during the three weeks after induction chemotherapy.

In the restaging after induction chemo-immunotherapy an endoscopy with biopsy will be performed (day 22-26). Before panendoscopy with biopsy, laboratory assessments of hematology, clinical chemistry, coagulation tests and TSH have to be performed. Furthermore an 12-lead ECG has to be done in advance. The paraffin-embedded biopsy is to be sent to the reference pathology at the university hospitals Erlangen for assessment of CD8 density.

Radiotherapy should start on day 29. If CD8 evaluation is not available, the beginning of radiotherapy can be delayed for one week or two weeks (if CD8 count is not completed and

finally validated). Consequently also the second administration of durvalumab and tremelimumab has to be delayed for one week or two weeks, respectively. In case of longer delay, the principal investigator has to be contacted.

Before starting the radiotherapy, a directed physical examination has to be performed.

At the last radiation the following procedures will be performed:

- ECOG performance status
- Review of concomitant medications
- Review of adverse events
- Full physical examination
- Vital signs and weight
- Patient questionnaires

Restaging will be performed twelve weeks after radiotherapy, i.e. after 4 doses of tremelimumab/durvalumab combination therapy and 2 doses of durvalumab monotherapy (week 23 in the schedule). Imaging of the neck will be performed with contrast enhanced CT and/or MRI. In addition a panendoscopy and, if clinically indicated, a biopsy is performed. Alternatively an FDG-PET/CT can be done if this is clinical routine in the treating center. In this case a panendoscopy with biopsy is only necessary, if local tumor persistence at the primary site is suspected. Before panendoscopy the following following procedures will be performed: laboratory assessments of hematology, clinical chemistry, coagulation tests and TSH have to be performed:

- Patient questionnaires
- Directed physical examination
- Hematology
- Clinical chemistry
- TSH

Patients with complete response will receive additional 6 cycles of durvalumab maintenance treatment. If there is residual persistent disease in the neck, a neck dissection is recommended. The extent of the neck dissection is at the discretion of the treating head and neck surgeon. In case of histologically confirmed local tumor persistence, salvage surgery should be planned at the discretion of the treating head and neck surgeon, if the patient is fit for the planned intervention and accepts the intervention and its potential side effects. Surgical specimens with residual tumor are to be submitted to the reference pathology at the university hospital Erlangen. If a complete tumor resection is possible with salvage surgery, the patient should also receive further 6 cycles of durvalumab maintenance treatment. In case of major surgery, the time period from the last durvalumab administration should be at least one week. After surgery durvalumab

maintenance should only be started when the wound healing is completed. In case of delayed wound healing durvalumab can be administered delayed up to 4 weeks (time period of one cycle). The following time intervals up to cycle 6 will be the usual q4w. In case of a longer delay, the principal investigator has to be contacted. If a complete tumor resection is not possible, the systemic treatment has to be changed. The decision which systemic treatment should be offered outside this trial is at the discretion of the treating physician and depends on the fitness of the patient.

8.1.4 End of Treatment

There are several time points of a possible End of Treatment:

- Patients without an increase of tumor infiltrating CD8+ immune cells or progressive disease after induction chemo-imunotherapy will be treated with a standard CRT or salvage surgery outside the trial. For these patients the panendoscopy with biopsy is the last procedure in the trial. The safety follow up must be performed also for these patients. The chosen standard CRT has to be documented and their survival status will be followed up.

- In patients with PD in the restaging after radioimmunotherapy or PR/SD that cannot be treated curative with salvage surgery, the restaging with CT or MRI is the last procedure in the treatment phase. The same applies to patients in which durvalumab +/- tremelimumab was stopped prior the restaging after radioimmunotherapy.

- If durvalumab has to be stopped in the maintenance phase, the last administration of durvalumab is the last procedure in the treatment phase.

- After administration of 4 cycles durvalumab + tremelimumab and additional 8 cycles of durvalumab also patients without progression or dose limiting toxicity end the trial.

A safety follow up will be performed 90 days after the last administration of durvalumab +/- tremelimumab or prior to start of next-line therapy, if earlier.

These procedures will be performed in the safety follow up:

- ECOG performance status
- Review of concomitant medications
- Review of adverse events
- Full physical examination
- Vital signs and weight
- Patient questionnaires

- Subsequent anti-cancer therapy
- Urine analysis
- Clinical laboratory tests for:
    - Highly sensitive serum pregnancy test (for women of childbearing potential only)
    - Hematology
    - Clinical chemistry
    - TSH
    - Blood for correlative studies (except before first administration)

Patients without tumor progression enter the follow up visits which will be performed every 12 weeks. Tumor assessment will be performed according the clinical standard in the respective treatment center. Adverse events and post-study anticancer therapy status will be reviewed at every visit and a directed physical examination performed. The maximal follow up period is 2 years after completion of radiotherapy.

After disease progression only a survival follow up will be performed every 12 weeks.

8.2 Description of study procedures

8.2.1 Medical history and physical examination, electrocardiogram, weight and vital signs

Findings from medical history (obtained at screening) and physical examination shall be given a baseline grade according to the procedure for AEs. Increases in severity of pre-existing conditions during the study will be considered AEs, with resolution occurring when the grade returns to the pre-study grade or below. Physical examinations will be performed on study days noted in the Schedule of Assessments.

8.2.2 Physical examination

Physical examinations will be performed according to the assessment schedule. Full physical examinations will include assessments of the head, eyes, ears, nose, and throat and the respiratory, cardiovascular, GI, urogenital, musculoskeletal, neurological, dermatological, hematologic/lymphatic, and endocrine systems. Height will be measured at screening only. Targeted physical examinations are to be utilized by the Investigator on the basis of clinical observations and symptomatology. Situations in which physical examination results should be reported as AEs are described in Section 10. In case of a previous history of bleeding or anticoagulant medications, each full or targeted physical examination has to include an oral inspection for bleeding signs and medical history of bleeding. Based on this information and

the hemoglobin value the investigator decides if the patient has to be transferred to a head and neck surgeon for further treatment.

8.2.3 Electrocardiograms

Resting 12-lead ECGs will be recorded at screening and before panendoscopy with biopsy and as clinically indicated throughout the study (see Schedule of Assessment). ECGs should be obtained after the patient has been in a supine position for 5 minutes and recorded while the patient remains in that position.

In case of clinically significant ECG abnormalities, including a QTcF value >470 ms, 2 additional 12-lead ECGs should be obtained over a brief period (e.g., 30 minutes) to confirm the finding.

Situations in which ECG results should be reported as AEs are described in Section 10.3.1.

8.2.4 Echocardiography

A transthoracic echocardiography must be performed in the screening phase to rule out cardiac insufficiency. Cardiac output must enable a sufficient hydration before and during the induction chemotherapy.

8.2.5 Dental check-up

A dental check-up is required for all patients in the screening phase. If clinically indicated, teeth should be extracted. This should be performed before the planning CT scan. Detailed information of the patients about dental care is recommended.

8.2.6 Endoscopy with biopsy

Endoscopy of the upper aero-digestive tract will be performed after the induction chemo-immunotherapy. A biopsy of the tumor is required for the assessment of the density of CD8+ tumor infiltrating immune cells. The endoscopy will be performed under general anesthesia. Exact descriptions and / or photographs should be performed to support the delineation of the GTV in the radiotherapy treatment planning.

A further endoscopy will be performed in the second restaging after radio-immunotherapy. Biopsy is optional, but should be performed if a residual primary tumor is suspected.

8.2.7 Vital signs

Vital signs (blood pressure [BP], pulse, temperature, and respiration rate) will be evaluated according to the assessment schedules. Body weight is also recorded at each visit along with vital signs.

First infusion

On the first infusion day, patients in the durvalumab + tremelimumab combination therapy group will be monitored and vital signs collected/recorded in eCRF prior to, during and after infusion of IP as presented in the bulleted list below.

BP and pulse will be collected from patients before, during, and after each infusion at the following times (based on a 60-minute infusion):

- Prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes [ie, the beginning of the infusion])
- Approximately 30 minutes during the infusion (**halfway** through infusion)
- At the end of the infusion (approximately 60 minutes ±5 minutes)

If the infusion takes longer than 60 minutes, then BP and pulse measurements should follow the principles as described above or be taken more frequently if clinically indicated. A 1-hour observation period is recommended after the first infusion of durvalumab and tremelimumab.

Subsequent infusions

BP, pulse and other vital signs should be measured, collected/recorded in eCRF prior to the start of the infusion. Patients should be carefully monitored and BP and other vital signs should be measured during and post infusion as per institution standard and as clinically indicated. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the Investigator's discretion (suggested 30 minutes after each durvalumab and tremelimumab infusion). Any clinically significant changes in vital signs should be entered onto an unscheduled vital signs CRF page.

8.2.8 Clinical laboratory tests

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken at the times indicated in the assessment schedules and as clinically indicated.

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

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection, and results (values, units, and reference ranges) will be recorded on the appropriate eCRF.

The laboratory variables to be measured are presented in the following tables.

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

The following laboratory variables will be measured:

Table 5. Clinical chemistry

Albumin	Lipase[b]
Alkaline phosphatase	Magnesium[c]
ALT[a]	Potassium
Amylase[b]	Sodium
AST[a]	Total bilirubin[a]
	Total protein
Calcium	TSH
Chloride[c]	T3 free[d] (reflex)
Creatinine clearance[c]	T4 free[d] (reflex)
Creatinine	Urea or blood urea nitrogen, depending on local practice
Gamma glutamyltransferase[c]	CRP
Glucose	
Lactate dehydrogenase	

[a] Tests for ALT, AST, alkaline phosphatase, and total bilirubin must be conducted and assessed concurrently. If total bilirubin is ≥2 × upper limit of normal (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin.

[b] It is preferable that both amylase and lipase parameters are assessed. For sites where only 1 of these parameters is routinely measured then either lipase or amylase is acceptable.

[c] Chloride, creatinine clearance (calculated), gamma glutamyltransferase, and magnesium testing are to be performed at screening, on Day 0 (unless screening laboratory assessments are performed within 3 days prior to Day 0), and if clinically indicated.

[d] Free T3 or free T4 will only be measured if TSH is abnormal or if there is a clinical suspicion of an AE related to the endocrine system

ALT Alanine aminotransferase; AST Aspartate aminotransferase, TSH Thyroid Stimulating Hormone

Table 6 Hematology

Platelet count	White blood cell count
Hemoglobin	Absolute lymphocyte count
Hematocrit	Absolute neutrophil count
Red Blood Cell count	Absolute eosinophil count
	Adolute basophil count
	Absolute monocyte count

Note: For coagulation parameters, activated partial thromboplastin time and international normalized ratio are to be assessed at baseline and as clinically indicated.

Table 7 Urinanalysis

Urinalysis should be done at baseline (screening) and then as clinically indicated

Bilirubin	Ketones
Blood	pH
Color and appearance	Protein
Glucose	Specific gravity

Note: Microscopy should be used as appropriate to investigate white blood cells and use the high power field for red blood cells.

8.2.9 Pregnancy testing in women of child bearing potential

A highly sensitive serum pregnancy test has to be performed in all women of child bearing potential (see section 7.1.1). The pregnancy test will be performed in the screening phase and a maximum time period of 72 hours before each administration of durvalumab and/or tremelimumab during the whole treatment period. Pregnancy testing has to be continued monthly up to 90 days after durvalumab monotherapy or 180 days after durvalumab plus tremelimumab combination therapy. This also applies to patients, who have only received one administration as induction treatment.

8.2.10 Patient reported outcomes (PRO)

Patient reported outcomes will be measured in the screening phase, at the last radiation, in the restaging after radiotherapy and in the safety follow-up (see the assessments schedule).

8.2.10.1 Quality of life

Quality of life will be measured with the EORTC QLQ-C30 questionnaire. In addition disease specific quality of life will be measured with the EORTC QLQ-H&N35 questionnaire.

8.2.10.2 Swallowing function

Patient reported dysphagia will be assessed with the EAT-10 questionnaire.

8.3 Biological sampling procedures

8.3.1 Tissue biomarker sampling and evaluation methods

8.3.1.1 Sample collection and processing for CD8 and PD-L1 testing

Sample collection for CD8 and PD-L1 testing

- CD8 and PD-L1 testing will be performed at the Institute of Pathology of the University Hospitals Erlangen for all patients. The existing pre-treatment biopsy will be shipped in the pre-screening phase and the biopsy of the first restaging immediately to the Institute of Pathology of the University Hospitals Erlangen.

- The preferred sample for PD-L1 testing has to be less than or equal to 3 months old. In cases where a sample less than 3 months old will not be available, patients will be asked to undergo a new biopsy if considered clinically appropriate by their treating physician.

- Samples will be collected via a core needle of 18 gauge or larger or be collected by an incisional or excisional tumor biopsy.

- Samples submitted for CD8 and PD-L1 testing will be formalin fixed and embedded in paraffin. Samples from fine needle aspirate (FNA) or decalcified bones are not appropriate for CD8 or PD-L1 analysis.

Sample data collection for CD8 and PD-L1 testing
The following fields of data will be collected from the site/institution collecting and if, indicated shipping of the samples:

- Patient identifier (encode or unique identifier)
- Specimen identifier (written on the specimen)
- Site identifier
- Specimen collection date

- Type of specimen submitted
- Quantity of specimen
- Date of sectioning
- Archival of fresh tumor
- Tumor type
- Primary tumor location
- Fixative

Sample processing and if indicated submission process for CD8 and PD-L1 testing

Preparing Stored samples for testing

- Where samples already exist, they will be retrieved from the Bio-Bank storage location or pathology archive. These blocks will undergo quality review, prior to evaluation or shipment. Where it is not possible or indicated to ship the block to a testing laboratory, unstained slides will be prepared from the paraffin-embedded tumor sample block (described below) prior to evaluation or shipment.

Preparing newly acquired samples for CD8 and PD-L1 testing

- If patients are undergoing a biopsy procedure that provides the option to submit newly acquired samples, this sample will be used to determine PD-L1 status. Where clinically acceptable, a minimum of 2 core biopsies will be collected and processed to FFPE in a single block.

- The core needle tumor biopsies are collected using an 18 gauge or larger needle and the process will be image-guided. Excisional or incisional samples are also possible. If available, a single excisional biopsy of at least 4 mm in diameter may substitute for all core biopsies.

Fixation of biopsy samples for CD8 and PD-L1 testing

- Previously frozen tissue is not acceptable for processing to FFPE for CD8 and PD-L1 testing. To fix newly acquired tissue, the tissue will be placed immediately (within 30 min of excision) into an adequate volume of 10% v/v neutral buffered formalin (NBF). Samples will remain in fixative for 24 – 48 hours at room temperature.

- It is vital that there is an adequate volume of fixative relevant to the tissue (at least a 10 volume excess) and that large specimens (if any) are incised prior to fixation to promote efficient tissue preservation.

Embedding in paraffin for CD8 and PD-L1 testing

- An overnight processing schedule into paraffin wax is envisaged

Storage of tumor blocks for CD8 and PD-L1 testing

- FFPE blocks will be stored at ambient temperature and protected from light until shipment by courier at ambient temperature. FFPE blocks are stable under these conditions for an indefinite period.

Quality control of samples to be used for CD8 and PD-L1 testing

- Tissue will be assessed by the site pathologist prior to PD-L1 testing.
- Each sample will be reviewed for:
    - Adequate fixation
    - Good preservation of morphology
    - Presence of tumor tissue
    - Histopathology consistent with indication
    - Greater than 100 tumor cells are required to determine CD8 and PD-L1 status – tumor cell content will be reviewed prior to testing in order for PD-L1 obtain a valid result.

Shipping samples to a CD8 and PD-L1 testing laboratory

- When submitting sample to for CD8 and PD-L1 testing the recommendation is to ship the block in order for sectioning to occur at the laboratory. Blocks will be shipped - containing enough material to be provided to allow a minimum of 5, and preferably 10, sections to be cut (each 4 microns thick) to be used for PD-L1 testing.

Sectioning instructions

- Where it is not possible or indicated to ship the block to laboratory for CD8 and PD-L1 testing, unstained slides will be prepared from the paraffin-embedded tumor sample block as described below:

- A minimum of 5-10 x 4 micron (µm) thick, unstained sections should be provided for CD8 and PD-L1 testing
- A new disposable microtome blade will be used for each block to prevent contamination between patient samples
- Slides are stable under these conditions for 6 months.
- One section per slide will be applied to positively-charged Superfrost glass slides
- The sections will be dried overnight between room temperature and 37°C. Temperatures above 37°C will be avoided.

Sections will be stored at ambient temperature and protected from light until use or shipment to testing lab by courier at ambient temperature. It is recommended that slides are cut freshly prior to CD8 and PD-L1 testing and they are used within 90 days of being cut to obtain CD8 and PD-L1 status.

8.3.1.2 CD8 testing

Slides will be stained on a Ventana Benchmark Ultra immunostainer using a monoclonal CD8 antibody with an accredited protocol. The number of CD8-positive immune cells infiltrating the tumor tissue will be quantitatively evaluated in an area of 2 to 5 mm² (depending on biopsy size). The antibody CD8 clone C8/144b (DAKO Omnis Agilent, Santa Clara, USA) will be used. This antibody is CE-IVD certified. The immunohistochemistry laboratory of the Institute of Pathology of the University Hospital is accredited according to ISO90210. Adequate positive on-slide controls (lymph node tissue) will be used on each slide. An H&E-stained slide will be analyzed in parallel for correct identification of tumor area. Density of CD8-positive tumor infiltrating cells will be counted by two experienced board certified pathologists, and will also be counted quantitatively after whole mount scan of stained slides using automated software.

The following fields of data will be collected from CD8 testing laboratory:

- Are the negative and positive controls stained correctly
- Is the H&E material acceptable
- Is morphology acceptable
- Semi-automatic quantitative detection of density of CD8 positive tumor infiltrating cells
- Restaging Biopsy: Comparison quantitative density of CD8 positive tumor infiltrating cells
- Visual confirmation and evaluation of two experienced pathologists if CD8 density is increased for at least 20% or not.

Based on the evaluation of a relevant increase of CD8 density (≥20%), patients can enter radioimmunotherapy or not. This cut-off value may be adjusted after the interim analysis.

8.3.1.3 PD-L1 testing

To ensure comparability of data across all studies of durvalumab and/or tremelimumab and to gain real world experience on the performance of this assay, we will utilize the Ventana SP263 assay for PD-L1 testing. Assays will be performed in accordance with the package insert on the Ventana Benchmark platform (Ultra or XT).

The Ventana SP263 assay is fully analytically validated test characterized through to the completion of reader precision studies in the non-small cell lung cancer (NSCLC) and squamous cell carcinoma of the head & neck (SCCHN). For these tumors, the Ventana SP263 assay has a fully reproducibility data package supporting cut-off and scoring algorithm. Following completion of ATLANTIC and HAWK clinical trials, the assay will be associated with clinical utility. In other cancer types (bladder, pancreatic, gastric, hepatocellular, triple negative breast, ovarian, esophageal, nasopharyngeal, glioblastoma, soft tissue sarcoma, cholangiocarcinoma, small cell lung, melanoma and cervical HPV + cancers), the Ventana SP263 assay has only limited clinical performance data.

The following fields of data will be collected from PD-L1 testing laboratory:

- Are the negative and positive controls stained correctly
- Is the H&E material acceptable
- Is morphology acceptable
- Total percent positivity of PD-L1 in tumor cells
- PD-L1 status (positive, negative or NA) in tumor cells
- Total percent positivity of PD-L1 in infiltrating immune cells

The Ventana SP263 assay to measure PD-L1 in tumors is experimental. As with all tests, there is a chance of false positive (the test shows high PD-L1 when it is not there) or false negative (the test does not show PD-L1 when it is there) results may occur.

8.3.2 Use of archival tumor samples beyond PD-L1 and CD8

8.3.2.1 HPV assessment via p16 testing

As mentioned above p16 positive tumors of the oropharynx respond better to radiotherapy and probably immunotherapy than p16 negative tumors. p16 immunohistochemistry will be performed for all patients according to the local standard approach of the treating center.

8.3.2.2 Interferon-gamma signature

IFN-gamma response genes ("10 gene analyses") will be performed in RNA extracted from tumor biopsies using quantitative real-time PCR. Expression of IFN-gamma response genes will be calculated in relation to reference genes using the delta-delta-Ct method.

8.3.2.3 Detailed immune status of the tumor

The immunosuppressive potential of a cancer is of great interest. PD-L1 is a major player in the immunosuppression of inflammatory cells, however there are several other potential immunosuppressive cells like regulatory T cells and M2 macrophages. Another question is whether the inflammatory cells like cytotoxic cells (CD8, M1 macrophages) or antigen presenting cells (dendritic cells, B cells) are functional or immunosuppressed. We have developed a multiparameter and multislice assay to analyze the immunosuppressive potential of the inflammatory cells and the functional activity of the antigen presenting and cytotoxic cells. We use serial sections of the tumor tissue sections and stain it mostly by double stainings as shown in Table 8. The overall set of slides is scanned by a whole slide scanner. By the use of an image analysis software each image is as accurately as possible aligned to each other. The tumor epithelium and stromal areas are identified and the inflammatory cells and tumor cells are marked by the software. The positions of the tumor and stromal mass and the coordinates of the inflammatory cells are transferred to a database. Now from these data sets the distribution pattern and the distance from each cell to the next cell can be calculated. The calculated cell to cell distances can be compared to simulated distances showing whether cells are randomly distributed and therefore not functional or have shorter distances than the simulated distances and are assessed to be functional due to their interactions with other inflammatory or tumor cells[104-106]. Additionally it is possible to calculate an immunosuppressive score or cytotoxicity score or other multiparameter scores.

Table 8: Multislice staining strategy

	Marker 1	Marker 2	Identified characteristics by marker 1	Identified characteristics by marker 2
1	H3K9me3		Premature senescence	
2	CleavedCaspae3	Ki67	Apoptosis	Proliferation
3	E-Cadherin	HE	Cell-in-cell, budding	Cancer cells
4	CD68	CD163	M1 macrophages (cytotoxic)	M2 macrophages (immunosuppressive)
5	FoxP3	CD8	Regulatory T cells	Cytotoxic T cells
6	PD-L1		Programmed death-ligand 1	
7	CD1a	CD20	Dendritic cells	B cells
8	CD45RO	CD4	Memory T cells	T helper cells
9	PD1		Programmed cell death protein 1	

8.3.3 Detailed peripheral blood immune status sampling and evaluation methods

Fresh whole blood, plasma and serum will be collected. Whole blood will be analyzed within 24h (over-night sample shipping) and plasma and serum will be collected and stored at -80°C in the quality-controlled in-house biobank.

A detailed immunophenotyping in patient's whole blood samples before, at several time points during and after therapy will be performed. A modular multicolor flow cytometry-based method has already been developed that allows the characterization of 34 subtypes of immune cells and their activation state including PD1, PD-L1 and CTLA-4 expression[99]. This should help to understand the mechanistic basis of the immune response after radiotherapy and combined PD-1/PD-L1 pathway and CTLA4-pathway blockade on a systemic level. This can be correlated to local events observed in the tumor biopsies.

The blood draws will be performed as scheduled in the study procedures:

1) After successful inclusion of the patient in the study to conserve the pretherapeutic stage

2) At the first restaging to get first hints about the effect of checkpoint blockade after systemic therapy with cisplatin/docetaxel in combination with durvalumab/tremelimumab

3) At the two following administrations of immune checkpoint inhibitors during radiotherapy and the first administration after radiotherapy to study immunological interactions with radiotherapy.

4) After the second restaging at cycle 7 and cycle 10 of durvalumab to elucidate if consecutive checkpoint blockade is able to perpetuate the induced immune effects. The long term and closely-meshed surveillance of the patients may further reveal immune-related side effects of long term checkpoint blockade.

5) In the safety follow up.

Sample collection will be performed by study physician at the given time points. The blood draws for the translational research program will be combined with routine blood draws to reduce the stress of the patients and to avoid an increased risk of blood draw side effects. The samples will be identified only by trial patient number and stored according to this identifier. Serum will be obtained from 9 ml of clotted whole blood. 7 ml of non-clotted blood (EDTA) will be used for the detailed immunophenotyping (3ml whole blood) and plasma collection. The remaining cells of the plasma collection will be stored in order to prepare DNA and RNA for possible future analyses

The immunophenotyping in whole blood of all patients will be performed by the Radiation Immunobiology Group at the Department of Radiation Oncology. The analyses will result in a detailed longitudinal follow-up over the whole therapy time of each patient and will reveal therapy-induced systemic immune modulations. The Department of Radiation Oncology will provide the complete technical equipment for the detailed immunophenotyping, namely a state-of-the-art 10-colour flow cytometer as well as the Kaluza software for analysis and data mining. In addition, all standard technical equipment of biomedical laboratories (centrifuges, ultra-cold fridge, laboratory space, building incidentals, office supplies and computing costs) is fully provided by the Department of Radiation Oncology.

To complete the analyses of the immune modulations induced by the local radiation therapy in combination with checkpoint blockade, we will collect and store serum and plasma of all patients at our in-house biobank. The analyses of soluble immune modulatory substances in serum and/or plasma (e.g. chemokines, cytokines, danger signals, and acute phase proteins) will enable to generate a cluster of biomarkers which can be correlated with the therapy outcome. These results can be combined with the results of the immunophenotyping to have a complete picture of the systemic immune modulations related to the radioimmunotherapy. The detection of 10 chemokines/cytokines and 2 prominent danger signals will be performed via sandwich ELISA. The patient's material that will be brought in by all treating centers for this study will be collected and stored at the Department of Radiation Oncology.

If a patient is excluded from the study the data of the biomaterial analyses till that time point will be retained as well as the stored blood samples.

Biobanking at Department of Radiation Oncology:

A biobank which allows storing of all blood samples (serum, plasma, DNA, and RNA) in a highly quality-controlled manner already exists. All samples will be processed in the Laboratory of Molecular and Cellular Radiobiology at the Department of Radiation Oncology and stored in 2D Matrix coded tubes. The samples will be managed with sample storage software [LIMS] which allows adding an audit trail to every sample. This enables the spreading of the samples to all partners for further analyses.

The technical equipment for the biobank system (ultra-cold fridges (temperature monitored 24/7), 2D plate barcode-scanner, centrifuges, LIMS software) is fully provided by the Department of Radiation Oncology. In addition all standard technical equipment of biomedical laboratories (centrifuges, ultra-cold fridge, laboratory space, building incidentals, office supplies and computing costs) is fully provided by the Department of Radiation Oncology.

8.3.4 Peripheral blood cell-free DNA sampling and evaluation methods (liquid biopsy)

Liquid biopsies will be taken at the scheduled time points during and after therapy. Both quantity and changes of genetic EGFR- and p53-alterations in circulating cell-free DNA will be studied using an established Next-Generation sequencing approach on a MiSeq sequencing machine. This may be a useful tool for tumor assessment in future. These studies may provide evidence to improve the timing of the application of the drugs and radiotherapy or identify better future predictive bio-markers.

8.3.5 Estimate of volume of blood to be collected

The total volume of blood that will be drawn from each subject in the translational research project is as follows:

Table 9. Volume of blood to be drawn from each subject at each time point

Assessment	Sample volume (mL)	No. of samples	Total volume (mL)
Paxgene tubes for ctDNA extractio	10 ml	1	10 ml
S-Monovetten for serum	9 ml	1	9ml
K3E Monovetten for EDT blood (for immunophenotyping, plasma and DNA/RNA preparation)	7ml	1	7ml
Total			26 ml

8.3.6 Withdrawal of informed consent for donated biological samples

If a subject withdraws consent to the use of donated samples, there will be no new samples taken from the moment of withdrawal except for standard routine. Due to organizational issues, it is not possible to destroy the already taken and analyzed samples.

9. DISEASE EVALUATION AND METHODS

The primary endpoint of the trial is feasibility of a radioimmunotherapy with durvalumab and tremelimumab. Toxicity will be assesses by a qualified designee according to CTCAE 4.0 at the time points of the assessments schedule.

A further primary endpoint is the predictive character of changes of CD8+ tumor infiltrating immune cells after induction chemo-immunotherapy. The density of CD8+ tumor infiltrating immune cells will be detected quantitatively before and after induction chemo-immunotherapy. CD8 staining and evaluation will be performed for all patients at the department of pathology of the university hospitals Erlangen. It is expected that approximately every other patient has an increased density of CD8+ tumor infiltrating immune cells after induction chemo-immunotherapy using a cut-off value of 20% increase of intratumoral CD8+ cell density compared to baseline. If necessary, this parameter will be adjusted after an interim analysis.

Secondary endpoints address the efficacy of a combined radioimmunotheapy after CD8 based patient selection. Overall survival, progression free survival and the pathologically confirmed response rate will be studied. All patients will receive tumor imaging (CT or MRI) 12 weeks after completion of radiotherapy and panendoscopy with biopsy. Alternatively a FDG-PET/CT can be performed, if this is clinical routine in the treating center. In this case a panendoscopy with biopsy is only necessary in case of local residual tumor. In case of residual neck disease, a neck dissection should be performed. If there is residual histologically confirmed tumor at the primary site, the possibility of salvage surgery should be evaluated. Further follow up imaging is performed according to the clinical routine at the treating site. A disease progression can either base on a progression in the imaging according to RECIST 1.1 criteria or on a histological confirmation.

10. ASSESSMENT OF SAFETY

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

10.1.1 Safety Parameters

10.1.1.1 Definition of adverse events

An adverse event is the development of an undesirable medical condition (other than progression of the malignancy under evaluation) or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea,

chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

10.1.2 Definition of serious adverse events

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

Results in death

Is immediately life-threatening

Requires in-patient hospitalization or prolongation of existing hospitalization

Results in persistent or significant disability or incapacity

Is a congenital abnormality or birth defect in offspring of the subject

Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above

The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the investigator(s) and communicated to AstraZeneca.

10.1.3 Durvalumab + tremelimumab adverse events of special interest

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring and rapid communication by the investigator to the sponsor. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product.

AESIs for durvalumab ± tremelimumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy. An immune-mediated adverse event (imAE) is defined as an AESI that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE

diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE.

If the Investigator has any questions in regards to an event being an imAE, the Investigator should promptly contact the Study Physician.

AESIs observed with durvalumab ± tremelimumab include:

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

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

- Pericarditis
- Sarcoidosis
- Uveitis
- Other events involving the eye and skin
- Hematological events
- Rheumatological events

- Vasculitis
- Non-infectious meningitis
- Non-infectious encephalitis.

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

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

Further information on these risks (eg. presenting symptoms) can be found in the current version of the durvalumab and tremelimumab Investigator's Brochures. More specific guidelines for their evaluation and treatment are described in detail in the Dosing Modification and Toxicity Management Guidelines (see appendix 1). These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to the study drug/study regimen by the reporting investigator.

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

Pneumonitis (ILD) investigation

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

- Physical examination

  - Signs and symptoms (cough, shortness of breath and pyrexia, etc.) including auscultation for lung field will be assessed.

- SpO2
  - Saturation of peripheral oxygen (SpO2)
- CT scan of the chest
- Other items
  - When pneumonitis (ILD) is suspected during study treatment, the following markers should be measured where possible:ILD Markers (KL-6, SP-D) and β-D-glucan

Additional Clinical chemistry: CRP, LDH

10.2 Assessment of safety parameters

10.2.1 Assessment of severity

Assessment of severity is one of the responsibilities of the investigator in the evaluation of AEs and SAEs. Severity will be graded according to the NCI CTCAE v4.03.
For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used.

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 10.2.1. A Grade 3 AE need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a nonserious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

10.2.2 Assessment of relationship

The relationship of AEs or SAEs to radiotherapy, docetaxel, cisplatin, carboplatin, durvalumab, or tremelimumab will be evaluated by the investigator of the treating site.

10.3 Recording of adverse events and serious adverse events

Adverse events will be recorded using a recognized medical term or diagnosis that accurately reflects the event. Adverse events will be assessed by the investigator for severity, relationship

to the investigational product, possible etiologies, and whether the event meets criteria of an SAE and therefore requires immediate notification to AstraZeneca/MedImmune Patient Safety.

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- The maximum CTCAE grade reported
- Changes in CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the IPs (yes or no)
- Action taken with regard to IPs
- Administration of treatment for the AE
- Outcome

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

- Date the AE met criteria for SAE
- Date the Investigator became aware of the SAE
- Seriousness criteria fulfilled
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Whether an autopsy was performed
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to other medication

- Description of the SAE

The grading scales found in the revised NCI CTCAE version 4.03 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE version 4.03 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

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

Adverse events and serious adverse events will be recorded from time of signature of informed consent, throughout the treatment period and including the follow-up period (90 days after the last dose of durvalumab + tremelimumab or durvalumab).

During the course of the study all AEs and SAEs should be proactively followed up for each subject. Every effort should be made to obtain a resolution for all events, even if the events continue after discontinuation/study completion.

The investigator is responsible for following all SAEs until resolution, until the subject returns to baseline status, or until the condition has stabilized with the expectation that it will remain chronic, even if this extends beyond study participation.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject must be reported accroding to Section 10.3.10 if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

10.3.2 Causality collection

The Investigator will assess causal relationship between the IPs and each AE and answer “yes” or “no” to the question “Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?”

For SAEs causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure, the causal relationship is implied as “yes.”

The most frequent AEs of durvalumab and tremelimumab are listed in Appendix 1.

10.3.3 Relationship to protocol procedures

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

- Protocol related: The event occurred due to a procedure or intervention that was described in the protocol for which there is no alternative etiology present in the patient's medical record.

- Not protocol related: The event is related to an etiology other than the procedure or intervention that was described in the protocol. The alternative etiology must be documented in the study patient's medical record.

10.3.4 Adverse events based on signs and symptoms

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

10.3.5 Adverse events based on examinations and tests

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

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

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

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

10.3.6 Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥3 × ULN together with total bilirubin >2 × ULN may need to be reported as SAEs (see Section 10.3.10). Please refer to Appendix 1 for further instruction on cases of increases in liver biochemistry and evaluation of Hy's law.

10.3.7 Disease progression

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

10.3.8 New cancers

The development of a new cancer should be regarded and reported as an SAE (see Section 10.3.10). New primary cancers are those that are not the primary reason for the administration of the IP and have been identified after the patient's inclusion in this study.

10.3.9 Deaths

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

- Death clearly resulting from disease progression should be reported to the Study Monitor/Physician at the next monitoring visit and should be documented in the eCRF in the Statement of Death page. It should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported as an SAE within 24 hours (see Section 10.3.10). It should also be documented in the Statement of Death page in the eCRF. The report should contain a comment regarding the co involvement of PD, if appropriate, and should assign main and contributory causes of death.
- Deaths with an unknown cause should always be reported as an SAE (see Section 10.3.10). It should also be documented in the Statement of Death page in the eCRF.

A post mortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results should be forwarded to AstraZeneca Patient Safety or its representative within the usual timeframes.

Deaths occurring after the protocol defined safety follow up period after the administration of the last dose of study drug should be documented in the Statement of Death page. If the death occurred as a result of an event that started after the defined safety follow up period and the event is considered to be due to a late onset toxicity to study drug, then it should also be reported as an SAE (see Section 10.3.10).

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

10.3.10 Reporting of serious adverse events

All SAEs will be reported to AstraZeneca, the Sponsor and Winicker Norimed, whether or not considered causally related to the investigational product, or to the study procedure(s) within **24 hours**. The report will be made by recording the necessary information in the eCRF. In the event that the system is unavailable, the paper SAE report form provided should be completed and submitted to Winicker Norimed (fax: +49 911 / 9260 80 4444, backup for Email: safety@winicker-norimed.com) either by electronic or paper media. In this case, the reports will be forwarded to AstraZeneca and the Sponsor within one working day by Winicker Norimed.

Once the eCRF is available again, all information will need to be entered and submitted via the system.

The reporting period for SAEs is the period immediately following the time that written informed consent is obtained through 90 days after the last dose of durvalumab + tremelimumab, durvalumab or until the initiation of alternative anticancer therapy. The investigator and/or Sponsor are responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements.

10.3.10.1 Reporting of deaths to AstraZeneca

All deaths that occur during the study or within the protocol-defined 90-day post-last dose of durvalumab + tremelimumab or durvalumab safety follow-up period must be reported to AstraZeneca via eCRF or by Winicker Norimed according to section 10.3.9.

10.3.11 Sponsor Responsibility for Evaluating and Reporting Adverse Events

In addition to the first evaluation of AEs that is performed by the Investigator, a second evaluation with respect to seriousness, causality and expectedness and a risk-benefit assessment is performed by the Sponsor.

All AEs will be reported to regulatory authorities, IRB/ IECs and investigators in accordance with all applicable global laws and regulations:

SUSARs will be reported to IRB/ IECs and competent authorities by Winicker Norimed as follows:

- Non-fatal and non-life-threatening SUSARs latest within 15 calendar days
- Fatal or life-threatening SUSARs latest within seven calendar days

All involved Investigators will also be informed by Winicker Norimed.

Furthermore an Annual Safety Report will be provided to IRB/ IECs and competent authorities by the Sponsor once a year or on request. This task maybe delegated to Winicker Norimed.

As Reference Safety Information the current version of the IB for durvalumab will be used.The Sponsor will provide AstraZeneca with individual case reports of SUSARs in parallel to reporting to the regulatory authorities (Email to DES (Patient Safety Data Entry Site (only if secure data exchange is in place) or Fax to DES). Furthermore blinded listings of SAEs including Suspected Serious Adverse Reactions (SSARs) will be provided quarterly (Email to DES (Patient Safety Data Entry Site (only if secure data exchange is in place) or Fax to DES).

10.3.12 Other events requiring reporting

10.3.12.1 Overdose

Use of durvalumab or tremelimumab in doses in excess of that specified in the protocol is considered to be an overdose. There is currently no specific treatment in the event of overdose of durvalumab or tremelimumab, and possible symptoms of overdose are not established.

- An overdose with associated AEs will be recorded as the AE diagnosis or symptoms in the relevant AE modules of the eCRF and in the Overdose eCRF module.
- An overdose without associated symptoms will only be reported in the Overdose eCRF module.

If an overdose of an AstraZeneca IP occurs in the course of the study, then the Investigator or other site personnel will inform Winicker Norimed (fax: +49 911 / 9260 80 4444, backup for Email: safety@winicker-norimed.com) either by electronic or paper media immediately, or **no later than 24 hours** of when he or she becomes aware of it. The reports will be forwarded to AstraZeneca and the Sponsor within one working day by Winicker Norimed.

The designated AstraZeneca representative will work with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with an SAE, the standard reporting timelines apply (see Section 10.3.10). For other overdoses, reporting must occur within 30 days.

10.3.12.2 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- Pregnancy discovered before the study subject has received any study drugs.
- Pregnancy of a female partner of male subject, providing there is no restriction of male subject fathering a child.

Maternal exposure

If a patient becomes pregnant during the course of the study, the IPs should be discontinued immediately.

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

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel should inform Winicker Norimed (fax: +49 911 / 9260 80 4444, backup for Email: safety@winicker-norimed.com) either by electronic or paper media within 1 day, ie, immediately, but **no later than 24 hours** of when he or she becomes aware of it. The reports will be forwarded to AstraZeneca and the Sponsor within one working day by Winicker Norimed.

The designated AstraZeneca representative will work with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 to 5 calendar days for SAEs and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

10.3.13 Paternal exposure

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

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

Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the Investigator must obtain the consent of the patient's partner. Therefore, the local study team should adopt the generic ICF template in line with local procedures and submit it to the relevant Ethics Committees (ECs)/Institutional Review Boards (IRBs) prior to use.

10.3.14 Data Safety Monitoring Committee (DSMC)

A DSMC will be established to review accumulating safety data during the course of the trial. The DSMC may recommend discontinuation of the trial or modification of the protocol for safety reasons at any time during the trial. The decision to terminate is taken by the sponsor together with the coordinating Investigator. The members of the DSMC will be chosen from different fields. The members will not be involved in the design of the study, its conduct other than through their role on the DSMC and will have no financial interest in the outcome of the study. The DSMC will have written operating procedures.

11. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

11.1 Description of analysis sets

11.1.1 Safety analysis sets

The population for the primary endpoint, i.e. feasibility rate, is defined as follows (Evaluable Analysis Set, EAS)):

- patients receiving the protocol treatment according to the planned schedule, until cycle 6 of antibody treatment,

and

- patients in which any of the DLT events according to section 6.3.3 of the protocol was observed, irrespective of the overall amount and time schedule of treatment received.

This deviation from the conventional intent-to-treat principle is justified by the fact that the inclusion of patients, who drop out early for other reasons than a DLT event, could lead to an artificial improvement of the feasibility rate.

As sensitivity analysis, a second, worst-case approach will include the FAS (see below), counting all patients as failures, who did not receive the protocol treatment according to the planned schedule, until cycle 6 of antibody treatment.

The population for all other (descriptive) safety analyses consists of all patients having received at least one application of protocol therapy.

11.1.2 Efficacy analysis set

The primary population for the efficacy analyses is the full analysis set (FAS), consisting of all patients with a CD8-increase in the second biopsy, who can enter radioimmunotherapy, according to the intent-to-treat principle. However, patients who were enrolled although they unequivocally did not fulfil major selection criteria of the trial a priori ("non-eligible"), will be excluded from the statistical analysis, in accordance with ICH recommendations. Also patients who cannot enter radioimmunotherapy due to a stable or decreased CD8-density in the second biopsy will be excluded. Only case reports will be provided for this group. The decision on exclusions will be made by the steering committee during a pre-analysis meeting in a blinded fashion with respect to the final outcome.

A per-protocol population will likewise be prospectively defined for sensitivity analyses. From this population, patients dropping out during the radiotherapy phase for reasons clearly not related to the protocol treatment and/or its toxicity and/or an unfavourable course of the underlying disease will be excluded. Again, these exclusions will be decided upon by the steering committee during a pre-analysis meeting in a blinded fashion with respect to the final outcome.

11.2 Methods of statistical analyses

11.2.1 Safety Analyses

The main objective of this phase II study is to assess, whether the experimental multimodal regimen at the chosen dosage shows a promising feasibility profile in the treatment of locally

advanced HNSCC with immune reaction. The **feasibility rate** is chosen as primary safety endpoint, i.e. the proportion of EAS patients receiving the protocol treatment according to the planned schedule (until cycle 6 of antibody treatment), without occurrence of at least one of the DLT events, as defined in section 6.3.3. This proportion will be presented with exact 90% and 95% confidence intervals.

All other safety parameters will be evaluated in an explorative or descriptive manner, providing proportions, means, medians, ranges, standard deviations and/or confidence intervals, if appropriate. The analyses will focus on the adverse events categorized and graded according to NCI CTCAE. Further details will be defined in the Statistical Analysis Plan.

11.2.2 Efficacy Analyses

All efficacy parameters will be evaluated in an explorative or descriptive manner, providing proportions, means, medians, ranges, standard deviations and/or confidence intervals, as appropriate.

If p values are calculated (e.g. for comparison of subgroups such as those defined by CD8+ cell changes), they will be presented explicitly without referring to hypotheses or a significance level. Usually, no error adjustment for multiple testing will be performed. Thus the p values will reflect the comparison-wise error and not the experiment-wise error. All p values will be two-sided if not stated otherwise.

Comparisons of the categorical data, e.g. response rates, will be performed using chi² test, Fisher's exact test or a trend test according to Cochran/Armitage, as appropriate. Secondary endpoints of time-to-event type, i.e. progression-free survival and overall survival, will be estimated according to Kaplan-Meier, and exploratively compared (between subgroups, or to historical data, according to section 2.1.2) using the logrank test[107,108]. Hazard ratios (with confidence intervals) will be derived from corresponding Cox proportional hazard models, eventually adjusting for important prognostic factors (sensitivity analysis).

If the Peto logrank test is not appropriate because of violation of the proportional hazard assumption[109], Gehan's generalization of the Wilcoxon rank sum test for censored data[110] may be applied, preferably in its modification by Peto[107] and Prentice[111], as a sensitivity analysis.

11.2.3 Interim analyses

The first interim analysis addresses the cut-off value for CD8+ cell density after induction chemo-immunotherapy. This analysis is performed after 30 patients have had the CD8 staining after induction chemo-immnotherapy. From the beginning of the trial till this interim analysis the cut-off value for entering radioimmunotherapy is an increase of intratumoral CD8+ cells of at least 20%. It is expected that approximately 50% of the patients will have a clinically relevant

immune activation (see section 11.3). The cut-off value of 20% increase will be adjusted using the median of the increase of intratumoral CD8+ cells of the first 30 patients.

The second interim analysis addresses safety. A descriptive analysis of (serious) adverse events is performed after 20 patients have a complete documentation until cycle 4 of combined durvalumab plus tremelimumab treatment. This interim analysis may allow for early termination of the trial in case of unexpected toxicities or unexpectedly high frequencies of severe AEs.

11.3 Determination of sample size

Conventional empirical phase I study designs in clinical oncology assume, that an antineoplastic treatment is not feasible, if an unacceptable toxicity occurs in more than 1 out of 3 or 4 patients; however, the occurrence of dose limiting toxicities (DLT) in 1/6 is accepted [112-115]. This leads to the conclusion that the limit of acceptance is considered to be around 20%.

A one-stage design for pilot studies according to Fleming[116] is applied. In summary, the trial design is based on the following assumptions:

- The experimental therapy would be rated as unacceptable, if the actual feasibility rate (= 1 – rate with DLT events) was only 65% or lower.
- On the other hand, the therapy regimen would be considered to be a promising candidate for further development, if the true feasibility rate amounted to 80% or more.
- Probability to accept the experimental therapy as well tolerable, in spite of a *true* feasibility rate of < 65% (i.e. rate with DLT > 35%): 5% (type I error)
- Probability to reject the experimental therapy as not sufficiently feasible (<65%), although the true feasibility rate is promising (> 80%): 20% (type II error, corresponding to a power of 80%).

According to these parameters **n = 56** patients evaluable for feasibility have to start radio-immunotherapy.

So far, the CD8 density after induction chemo-immunotherapy has not been addressed in prior clinical trials. PD-1 inhibitors have shown clinical response rates in second line therapy of recurrent and/or metastatic HNSCC in 13-18%. Further 20-23% have stable disease[2,38]. Consequently, the disease control rate is approximately 37%. It is expected, that these patients with clinical benefit have an increased CD8 density in the tumor. An increase of CD8 tumor infiltrating immune cells has been demonstrated in biopsies from melanoma patients responding

to PD-1 blockade compared to non-responders[75]. In melanoma patients addition of CTLA-4 blockade to PD-1 blockade improved the disease control rate from 55% to 71%[90]. In the phase II HAWK trial (n=112), Durvalumab led to a response rate of 16.2% with additional 9.0% of patients with stable disease[117] in the recurrent/metastatic situation after progression to first line chemotherapy. But remarkable 40% of the patients had a decrease in their monitored target lesions. A limitation of this study is that all patients were PD-L1 positive. In this trial patients receive platinum-based chemotherapy before immunotherapy. In a recent analysis in HNSCC patients, platinum-based chemotherapy increased PD-L1 expression in 69% of prior PD-L1 negative patients[98]. The combination of chemotherapy and immunecheckpoint-inhibitors is highly effective in other tumor entities. A randomized phase III trial revealed a great success when pembrolizumab was added to chemotherapy in metastatic lung adenocarcinoma, which will probably change first line treatment[118]. Furthermore it is essential to know that in the HAWK trial patients were heavily pretreated as progression to platinum-based treatment in a recurrent and/or metastatic situation was inclusion criterion. In first line treatment, the response rates are probably higher. The main difference is that in the planned trial durvalumab is combined with tremelimumab. Taken together, it is strongly expected that the combination of induction chemotherapy and durvalumab and the addition of tremelimumab result in a higher rate of tumor control (CR, PR and SD). Based on these clinical findings an immunological treatment response or stable disease in approximately 50% of the patients is expected. Patients with treatment response or stable disease should have an increased intratumoral CD8+ cell density after induction treatment. Consequently, approximately 50% of the patients should have an increase in intratumoral CD8+ cells in the biopsy after induction treatment. These patients can enter radio-immunotherapy in this trial. Consequently, approximately double the number of patients entering radiotherapy (n = 56) are necessary to enter induction chemo-immunotherapy (n = 112).

In order to allow some non-informative drop-outs, a **total number of 120 patients** should be recruited. The final conclusion of the trial will depend on the definite feasibility rate (and its confidence interval), the efficacy endpoints as well as the complete information on type, frequency and severity of toxicities.

11.4 Additional statistical considerations after Amendment 3 (Expansion cohorts)

After amendment 3 the administration of the total tremelimumab dose of 300mg (absolute dose) will change from four doses of 75mg q4w (“Main Cohort”) to a single dose of 300mg (“Expansion cohort 1”). The “Expansion Cohort 2” studies the toxicity of Durvalumab without Tremelimumab within the treatment scheme of the CheckRad-CD8 trial. Data from a phase I/II trial indicate a similar safety of durvalumab 1500mg q4w combined with tremelimumab 300mg single dose or four doses of tremelimumab 75mg q4w (Study D4190C00022, ClinicalTrials.gov Identifier: NCT02519348). The primary endpoint of the trial is the feasibility rate until cycle six of immunotherapy (i.e. two cycles after the last dose of tremelimumab according to the study scheme before amendment 3). This endpoint will be studied in the “Main Cohort”. Recruitment

to the main cohort will be completed after the n=56 patients entered radioimmunotherapy. Due to the changed administration schedule of tremelimumab in the "Expansion Cohort 1", the toxicity of this tremelimumab dosing scheme will be analysed separately. Equally, the toxicity in the "Expansion Cohort 2" without Tremelimumab will be analyzed separately. The planned accurral for each expansion cohort is n=20 patients, which is a reasonable number of subjects for expansion cohorts in early clinical trials [119]. The feasibility rate for the entire cohort will only be calculated if no or only minor differences between the treatment groups exist that are not clinically relevant. If major or clinically relevant differences between the treatment cohorts appear, no pooled analysis of the groups will be performed and the final results for feasibility of the trial will be presented in the separated groups. Clinical procedures (schedule of assessments) including pathological assessment and treatment allocation will continue as scheduled. In order to guarantee the patients' safety, adverse events will be monitored in all treatment groups separately and in the entire cohort. In the translational research project, patients with four doses tremelimumab will be compared to patients with a single high dose of tremelimumab and patients without tremelimumab regarding peripheral blood immune phenotype and additional pathologic parameters.

12. ETHICAL AND REGULATORY REQUIREMENTS

12.1 Ethical conduct of the study

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

12.2 Ethics and regulatory review

All the documents required by the national law and other informative documents that may be requested will be submitted for review to an independent Ethics Committee whose procedures and operations meet the national legal requirements.

Selection of patients will not start before favorable opinion of the Ethics Committee has been obtained.

12.3 Informed consent

Information must be given to the patients providing the common features of the research as well as options of alternative possibilities of therapy. Restraints and risks must be explained, as well as the right to refuse or discontinue participation in the study at any stage, without further affecting the relationship to the investigator and/or their future care.

These written information and consent form will be submitted to the patient with an orally explanation. Only if the patient and the responsible investigator or a designee signs the consent form, the patient can enter the study.

12.4 Changes to the protocol and informed consent form

Substantial changes to protocol or patient information or informed consent form have to be approved by the Ethics Committee before use. All versions have to be kept in the Trial Master File.

12.5 Audits and inspections

By signing the protocol, the investigator agrees to conduct the trial in conformance with this protocol. The investigator also agrees to allow monitoring, audits, IRB/ERC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

13. STUDY MANAGEMENT

13.1 Training of study site personnel

Study personnel will be informed about the trial and the conduct of the study by in-house training by the investigator. The study protocol and other information about the IP and the study will be provided. Forms for collecting source data will be available at the visits of the patients. Standard Operating Procedures will be established and available to all study personnel.

13.2 Monitoring of the study

For all data entered in the case report form there has to be source data in the patient record. Trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice. The monitoring reviews clinical data for accuracy, completeness and consistency. Data are verified versus source data.

13.3 Study timetable and end of study

Table 10: Study timetable

Contract execution to ethics committee approval	6 months
Ethics committee approval to first subject in	3 months
First subject in to 50% enrollment	14 months

50% enrollment to last subject in	10 months
Last subject in to last subject last visit	27 months
Last subject last visit to completion of final study report	12 months

The estimated recruitment is approximately 6 patients per month.

14. DATA MANAGEMENT AND STUDY GOVERNANCE

14.1 Data management

All patient-related data are recorded in a pseudonymized way. Each patient is unequivocally identified by a trial subject number, attributed at inclusion in the study. The investigator has to keep a patient identification log, including the full name and address of the subject and eventually additional relevant personal data such as hospital record number, home physician etc. All patients, including those, who were screened in order to be entered into the study, but who could not be recruited for whatever reason (i.e. informed consent not given, not fulfilling selection criteria etc.) are recorded in a “patient screening log”.

All data retrieved during the conduct of the study are to be entered into the appropriate case record forms by the investigator or a qualified designee. The data has to be plausible and complete. All data fields have to be filled, except those referring to open questions. If a specific test was not performed or an information item is definitely not available or applicable, information on this should be provided (not done= nd; not applicable= na; unknown= uk). If a value or date is not known exactly, please explain in the comment field. There has to be source data for all data entered in the CRF.

The investigator is obliged to complete the case report forms within a reasonable time period after retrieval of the data (i.e. usually within 2 weeks). The study office or the monitor checks the forms for completeness and plausibility. In case of queries the monitor will send queries. The investigator or a designee is responsible for clarification/correction/completion in an appropriate time span.

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally vinding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

After finalization of the data checks by the study office/monitor the file or the database is locked.

All relevant study documents including the CRFs and patient source data are stored at the investigator for at least 10 years after completion of the final study report, eventually even longer according to regulatory or legal orders.

14.2 Study governance and oversight

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the study protocol and letters to Investigators.

15. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

15.1 Identity of investigational product(s)

Table 11. List of investigational products for this study

Investigational product	Dosage form and strength	Manufacturer
Durvalumab	*50 mg/mL solution for infusion after dilution*	MedImmune
Tremelimumab	*20 mg/mL solution for infusion after dilution*	MedImmune

The following manufacturers are relevant for the investigational products of the trial:

Durvalumab:

- DS is manufactured at AZ Frederick Maryland
- DP is manufactured at Cook Pharmica (now owned by Catalent) in Bloomington Indiana
- Generic labeling is performed at Fisher Clinical Services in Horsham UK
- QP certification of bulk unlabeled vials is performed by MedImmune Cambridge
- QP certification of generically labeled IMP is performed by AZ Macclesfield

Tremelimumab:

- DS and DP are manufactured by Boehringer Ingelheim in Baden-Wuerttemberg Germany

- Generic labeling is performed at Fisher Clinical Services in Horsham UK
- QP certification of bulk unlabeled vials is performed by MedImmune Cambridge
- QP certification of generically labeled IMP is performed by AZ Macclesfield

16. LITERATURE

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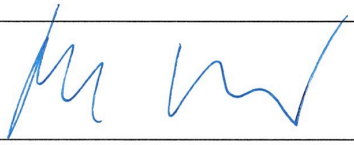
17. SIGNATURES

17.1 Sponsor´s Representative

TYPED NAME	MARKUS NEURATH
TITLE	Prof. Dr. Sponsor Dean of the Medical Faculty of the Friedrich-Alexander University Erlangen-Nürnberg
SIGNATURE	
DATE SIGNED	17.12.2020

TYPED NAME	MARKUS HECHT
TITLE	PD Dr. Principal Investigator
SIGNATURE	
DATE SIGNED	17. 12. 2020

17.2 Investigator

I agree to conduct this clinical trial in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol). I agree to conduct the trial in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events as defined in the section in the protocol. I also agree to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's Brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the trial is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

Clinical Study Protocol

Drug Substance Durvalumab (MEDI4736), Tremelimumab, Docetaxel, Cisplatin, Carboplatin

Study Number **ESR-16-12356;** Edition Number **Version 1.5;** Date **01.12.2020**

Appendix 1

Clinical Study Protocol

Drug Substance Durvalumab (MEDI4736), Tremelimumab, Docetaxel, Cisplatin, Carboplatin

Study Number **ESR-16-12356;** Edition Number **Version 1.5;** Date **01.12.2020**

Dosing Modification and Toxicity Management Guidelines (TMGs) for Durvalumab Monotherapy, Durvalumab in Combination with other Products, or Tremelimumab Monotherapy – 17 November 2020

General Considerations Regarding Immune-Mediated Reactions

These guidelines are provided as a recommendation to support investigators in the management of potential immune-mediated adverse events (imAEs).

Immune-mediated events can occur in nearly any organ or tissue, therefore, these guidelines may not include all the possible immune-mediated reactions. Investigators are advised to take into consideration the appropriate practice guidelines and other society guidelines (e.g., NCCN, ESMO) in the management of these events. Refer to the section of the table titled "Other -Immune-Mediated Reactions" for general guidance on imAEs not noted in the "Specific Immune-Mediated Reactions" section.
Early identification and management of immune-mediated adverse events (imAEs) are essential to ensure safe use of the study drug. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse events. Patients with suspected imAEs should be thoroughly evaluated to rule out any alternative etiologies (e.g., disease progression, concomitant medications, infections). In the absence of a clear alternative etiology, all such events should be managed as if they were immune-mediated. Institute medical management promptly, including specialty consultation as appropriate. In general, withhold study drug/study regimen for severe (Grade 3) imAEs. Permanently discontinue study drug/study regimen for life-threatening (Grade 4) imAEs, recurrent severe (Grade 3) imAEs that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating corticosteroids.

Based on the severity of the imAE, durvalumab should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1, corticosteroid should be tapered over ≥ 28 days. More potent immunosuppressive agents such as TNF inhibitors (e.g., infliximab) should be considered for events not responding to systemic steroids. Alternative immunosuppressive agents not listed in this guideline may be considered at the discretion of the investigator based on clinical practice and relevant guidelines. With long-term steroid and other immunosuppressive use, consider need for *Pneumocystis jirovecii* pneumonia (PJP, formerly known as *Pneumocystis carinii* pneumonia) prophylaxis, gastrointestinal protection, and glucose monitoring.

Dose modifications of study drug/study regimen should be based on severity of treatment-emergent toxicities graded per NCI CTCAE version in the applicable study protocol.

AE Adverse event; CTC Common Toxicity Criteria; CTCAE Common Terminology Criteria for Adverse Events; imAE immune-mediated adverse event; NCI National Cancer Institute; NCCN National Comprehensive Cancer Network; ESMO European Society for Medical Oncology

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
Pneumonitis/Interstitial Lung Disease (ILD)	**Any Grade** (NCI CTCAE v4.03)	**General Guidance**	**For Any Grade** – Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Evaluate patients with imaging and pulmonary function tests, including other diagnostic procedures as described below. – Suspected pneumonitis should be confirmed with radiographic imaging and other infectious and disease-related aetiologies excluded, and managed 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. – Consider Pulmonary and Infectious Diseases consults.
	Grade 1	No dose modifications required. However, consider holding study drug/study regimen dose as clinically appropriate and during diagnostic work-up for other etiologies.	**For Grade 1** – Monitor and closely follow up in 2 to 4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory work-up, and then as clinically indicated.
	Grade 2	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper.	**For Grade 2** – Monitor symptoms daily and consider hospitalization. – Promptly start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent). – Reimage as clinically indicated, consider chest CT with contrast and repeat in 3-4 weeks. – If no improvement within 2 to 3 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started.

			– If no improvement within 2 to 3 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV once, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. Consider, as necessary, discussing with study physician.
	Grade 3 or 4	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Obtain Pulmonary and Infectious Diseases Consults; consider discussing with study physician, as needed. – Hospitalize the patient. – Supportive care (e.g., oxygen). – If no improvement within 2 to 3 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab.
Diarrhea/Colitis	**Any Grade** (NCI CTCAE v4.03)	**General Guidance**	**For 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). – **WHEN SYMPTOMS OR EVALUATION INDICATE AN INTESTINAL PERFORATION IS**

		SUSPECTED, CONSULT A SURGEON EXPERIENCED IN ABDOMINAL SURGERY IMMEDIATELY WITHOUT ANY DELAY. – **PERMANENTLY DISCONTINUE STUDY DRUG FOR ANY GRADE OF INTESTINAL PERFORATION.** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or 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 events, including intestinal perforation. – Use analgesics carefully; they can mask symptoms of perforation and peritonitis.
Grade 1	No dose modifications.	**For Grade 1** – Monitor closely for worsening symptoms. – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), loperamide, and other supportive care measures. – If symptoms persist,consider checking lactoferrin; if positive, treat as Grade 2 below. If negative and no infection, continue Grade 1 management.
Grade 2	Hold study drug/study regimen until resolution to Grade ≤1 • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then study drug/study regimen can be resumed after completion of steroid taper.	**For Grade 2** – 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 PO or IV equivalent. – If event is not responsive within 2 to 3 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consult a

		GI specialist for consideration of further workup, such as imaging and/or colonoscopy, to confirm colitis and rule out perforation. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg IV methylprednisolone, promptly start immunosuppressants such as infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider. [a] **Caution:** it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Consider, as necessary, discussing with study physician if no resolution to Grade ≤1 in 3 to 4 days.
Grade 3 or 4	**Grade 3** • For patient treated with PDL-1 inhibitors, hold study drug/study regimen until resolution to Grade ≤1; study drug/study regimen can be resumed after completion of steroid taper. Permanently discontinue study drug/study regimen for Grade 3 if toxicity does not improve to Grade ≤1 within 14 days. • Permanently discontinue study drug for 1) Grade 3 colitis in patients	**For Grade 3 or 4** – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – Monitor stool frequency and volume and maintain hydration. – Urgent GI consult and imaging and/or colonoscopy as appropriate. – If still no improvement within 2 days, continue steroids and promptly add further immunosuppressants (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). **Caution**: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – **If perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay.**

		treated with CTLA-4 inhibitors or 2) Any grade of intestinal perforation in any patient treated with ICI. **Grade 4** Permanently discontinue study drug/study regimen.	
Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis.	**Any Grade** (NCI CTCAE v4.03)	**General Guidance**	**For Any Grade** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications).
	Grade 1	• No dose modifications. • If it worsens, then treat as Grade 2.	**For Grade 1** – Continue LFT monitoring per protocol.
	Grade 2	• Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1 or baseline, resume study drug/study regimen after completion of steroid taper. • Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (AST and/or ALT >3 × ULN + bilirubin >2 × ULN without initial findings of cholestasis (i.e.,	**For Grade 2** – Regular and frequent checking of LFTs (e.g., every 1 to 2 days) until LFT elevations improve or resolve. – If no resolution to Grade ≤1 in 1 to 2 days, consider discussing with study physician, as needed. – If event is persistent (>2 to 3 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent.

		elevated alkaline P04) and in the absence of any alternative cause.[b]	
	Grade 3 or 4	**For Grade 3** For elevations in transaminases ≤8 × ULN, or elevations in bilirubin ≤5 × ULN: • Hold study drug/study regimen dose until resolution to Grade ≤1 or baseline • Resume study drug/study regimen if elevations downgrade to Grade ≤1 or baseline within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade to Grade ≤1 or baseline within 14 days • For elevations in transaminases >8 × ULN or elevations in bilirubin >5 × ULN, discontinue study drug/study regimen. **For Grade 4** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with an immunosuppressants (e.g., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** – Perform Hepatology Consult, abdominal workup, and imaging as appropriate.
Nephritis or renal dysfunction (elevated serum creatinine)	**Any Grade** (NCI CTCAE v4.03)	**General Guidance**	**For Any Grade** – Consult a nephrologist. – Monitor for signs and symptoms that may be related to changes in renal function (e.g., routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte

		imbalance, decreased urine output, or proteinuria). – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections, recent IV contrast, medications, fluid status). – Consider using steroids in the absence of a clear alternative etiology even for low-grade events (Grade 2), in order to prevent potential progression to higher grade events.
Grade 1	No dose modifications.	**For Grade 1** – Monitor serum creatinine weekly and any accompanying symptoms. • If creatinine returns to baseline, resume its regular monitoring per study protocol. • If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4. – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics.
Grade 2	Hold study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3 or 4. • If toxicity improves to Grade ≤1 or baseline, then resume study drug/study regimen after completion of steroid taper.	**For Grade 2** – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. – Carefully monitor serum creatinine every 2 to 3 days and as clinically warranted. – Consult nephrologist and consider renal biopsy if clinically indicated. – If event is persistent beyond 3 to 5 days or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consider additional workup.When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.

	Grade 3 or 4	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Carefully monitor serum creatinine daily. – Consult nephrologist and consider renal biopsy if clinically indicated. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consider additional workup and prompt treatment with an immunosuppressant in consultation with a nephrologist.
Rash or Dermatitis **(Including Pemphigoid)**	**Any Grade** (NCI CTCAE v4.03)	**General Guidance**	**For Any Grade** – Monitor for signs and symptoms of dermatitis (rash and pruritus). – **HOLD STUDY DRUG IF STEVENS-JOHNSON SYNDROME (SJS), TOXIC EPIDERMAL NECROLYSIS (TEN), OR OTHER SEVERE CUTANEOUS ADVERSE REACTION (SCAR) IS SUSPECTED.** – **PERMANENTLY DISCONTINUE STUDY DRUG IF SJS, TEN, OR SCAR IS CONFIRMED.**
	Grade 1	No dose modifications.	**For Grade 1** – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., emolient, lotion, or institutional standard).
	Grade 2	For persistent (>1 week) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3. • If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after	**For Grade 2** – Obtain dermatology consult. – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy – Consider moderate-strength topical steroid. – If no improvement of rash/skin lesions occurs within 3 days or

		completion of steroid taper.	is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider discussing with study physician, as needed, and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent. – Consider skin biopsy if the event persists for >1 week or recurs.
	Grade 3 or 4	**For Grade 3** • Hold study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper. • If toxicity worsens, then treat as Grade 4. **For Grade 4** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Consult dermatology. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – Consider hospitalization. – Monitor extent of rash [Rule of Nines]. – Consider skin biopsy (preferably more than 1) as clinically feasible. Consider, as necessary, discussing with study physician.
Endocrinopathy (e.g., hyperthyroidism, thyroiditis, hypothyroidism, type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency)	**Any Grade** (NCI CTCAE v4.03)	**General Guidance**	**For Any Grade** – Consider consulting an endocrinologist for endocrine events. – Consider discussing with study physician, as needed. – Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behaviour changes, mental status changes, photophobia, visual field cuts, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension, and weakness. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g.,

			disease progression including brain metastases, or infections). – Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, HgA1c).If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing. – Investigators should ask subjects with endocrinopathies who may require prolonged or continued hormonal replacement, to consult their primary care physicians or endocrinologists about further monitoring and treatment after completion of the study.
Grade 1	No dose modifications.		**For Grade 1** – Monitor patient with appropriate endocrine function tests. – For suspected hypophysitis/hypopituitarism, consider consulting an endocrinologist to guide assessment of early-morning ACTH, cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency). – If TSH < 0.5 × LLN, or TSH >2 × ULN, or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider consultation of an endocrinologist.
Grade 2, 3, or 4	• For Grade 2-4 endocrinopathies other than hypothyroidism		**For Grade 2, 3, or 4** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by

		and type 1 diabetes mellitus, consider holding study drug/study regimen dose until acute symptoms resolve. • Study drug/study regimen can be resumed once patient stabilizes and after completion of steroid taper. • Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen if the patient is clinically stable as per investigator or treating physician's clinical judgement. • If toxicity worsens, then treat based on severity.	suspected endocrinopathy and as clinically indicated, consider pituitary scan. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or type 1 DM, and as guided by an endocrinologist, consider short-term corticosteroids (e.g., 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g., hydrocortisone, sex hormones). – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated type 1 diabetes mellitus (DM) may be treated with appropriate diabetic therapy, and without corticosteroids. **Only hold study drug/study regimen in setting of hyperglycemia when diagnostic workup is positive for diabetic ketoacidosis**. – For patients with normal endocrine workup (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated.
Amylase/Lipase increased	**Any Grade** (NCI CTCAE v4.03) **Grade 1** **Grade 2, 3, or 4**	**General Guidance** No dose modifications. **For Grade 2, 3, or 4** In consultation with relevant pancreatic specialist consider continuing study drug/study regimen if no clinical/radiologic evidence of pancreatitis ± improvement in amylase/lipase.	**For Any Grade** – For modest asymptomatic elevations in serum amylase and lipase, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation. – Assess for signs/symptoms of pancreatitis – Consider appropriate diagnostic testing (e.g., abdominal CT with contrast, MRCP if clinical suspicion of pancreatitis and no radiologic evidence on CT) – If isolated elevation of enzymes without evidence of pancreatitis, continue immunotherapy. Consider

			other causes of elevated amylase/lipase – If evidence of pancreatitis, manage according to pancreatitis recommendations
Acute Pancreatitis	**Any Grade** (NCI CTCAE v4.03)	**General Guidance**	**For Any Grade** – Consider Gastroenterology referral
	Grade 1	No dose modifications.	**For Grade 1** – IV hydration – Manage as per amylase/lipase increased (asymptomatic)
	Grade 2, 3, or 4	**For Grade 2** Hold study drug/study regimen dose until resolution to Grade ≤1. **For Grade 3 or 4** Permanently discontinue study drug/study regimen.	**For Grade 2, 3, or 4** – Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. – IV hydration
Neurotoxicity (to include but not limited to non-infectious meningitis, non-infectious encephalitis, and autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	**Any Grade** (NCI CTCAE v4.03)	**General Guidance**	**For Any Grade** – Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes, or medications). – Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness). – Consider appropriate diagnostic testing (e.g., electromyogram and nerve conduction investigations). – Perform symptomatic treatment with neurological consult as appropriate. – **FOR TRANSVERSE MYELITIS, PERMANENTLY DISCONTINUE FOR ANY GRADE.**
	Grade 1	No dose modifications.	**For Grade 1**

			– See "Any Grade" recommendations above.
	Grade 2	• For acute motor neuropathies or neurotoxicity, hold study drug/study regimen dose until resolution to Grade ≤1. • For sensory neuropathy/neuropathic pain, consider holding study drug/study regimen dose until resolution to Grade ≤1. • Permanently discontinue study drug/study regimen if Grade 2 imAE does not resolve to Grade ≤1 within 30 days. • If toxicity worsens, then treat as Grade 3 or 4.	**For Grade 2** – Consider, as necessary, discussing with the study physician. – Obtain neurology consult. – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). – Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If no improvement within 2 to 3 days despite 1 to 2 mg/kg/day prednisone PO or IV equivalent, consider additional workup and promptly treat with an additional immunosuppressant (e.g., IV IG or other immunosuppressant depending on the specific imAE).
	Grade 3 or 4	**For Grade 3 or 4** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Consider, as necessary, discussing with study physician. – Obtain neurology consult. – Consider hospitalization. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – If no improvement within 2 to 3 days despite IV corticosteroids, consider additional workup and promptly treat with an additional immunosuppressant (e.g., IV IG or other immunosuppressant depending on the specific imAE). – Once stable, gradually taper steroids over ≥28 days.
Peripheral neuromotor syndromes (such as Guillain-Barre and myasthenia gravis)	**Any Grade** (NCI CTCAE v4.03)	**General Guidance**	**For Any Grade** – The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations that can

		result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms that 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 or medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor 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. – It is 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 IV IG and followed by plasmapheresis if not responsive to IV IG.
Grade 1	No dose modifications.	**For Grade 1** – Consider discussing with the study physician, as needed. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Consult a neurologist.

Grade 2	Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability.	**For Grade 2** – Consider discussing with the study physician, as needed. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Consult a neurologist. – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. It is 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 IV IG. 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 is present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. o Avoid medications that can worsen myasthenia gravis. *GUILLAIN-BARRE:*

		○ It is 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 IV IG and followed by plasmapheresis if not responsive to IV IG.
Grade 3 or 4	**For Grade 3** • Hold study drug/study regimen dose until resolution to Grade ≤1. • Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability. **For Grade 4** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Consider discussing with study physician, as needed. – Recommend hospitalization. – Monitor symptoms and consult a neurologist. *MYASTHENIA GRAVIS:* ○ Steroids may be successfully used to treat myasthenia gravis. They should typically be administered in a monitored setting under supervision of a consulting neurologist. ○ Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. ○ If myasthenia gravis-like neurotoxicity present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. ○ Avoid medications that can worsen myasthenia gravis. *GUILLAIN-BARRE:* ○ It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not

			typically considered effective. o Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
Myocarditis	**Any Grade** (NCI CTCAE v4.03)	**General Guidance** Discontinue drug permanently if biopsy-proven immune-mediated myocarditis.	**For Any Grade** – The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function. – Consider discussing with the study physician, as needed. – Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (e.g., pulmonary embolism, congestive heart failure, malignant pericardial effusion). Consult a cardiologist early, to promptly assess whether and when to complete a cardiac biopsy, including any other diagnostic procedures. – Initial work-up should include clinical evaluation, BNP, cardiac enzymes, ECG, echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory work-up as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections)
	Grade 1	No dose modifications required unless clinical suspicion is high, in which	**For Grade 1** - Monitor and closely follow up in 2 to 4 days for clinical symptoms, BNP, cardiac

		case hold study drug/study regimen dose during diagnostic work-up for other etiologies. If study drug/study regimen is held, resume after complete resolution to Grade 0.	enzymes, ECG, ECHO, pulse oximetry (resting and exertion), and laboratory work-up as clinically indicated. - Consider using steroids if clinical suspicion is high.
	Grade 2, 3 or 4	• If Grade 2 -- Hold study drug/study regimen dose until resolution to Grade 0. If toxicity rapidly improves to Grade 0, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper. If toxicity does not rapidly improve, permanently. discontinue study drug/study regimen. • If Grade 3-4, permanently discontinue study drug/study regimen.	**For Grade 2-4** – Monitor symptoms daily, hospitalize. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy. – Supportive care (e.g., oxygen). – If no improvement within 2 to 3 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. Infliximab is contraindicated for patients who have heart failure.**
Myositis/ Polymyositis	**Any Grade** (NCI CTCAE v4.03)	**General Guidance**	**For Any Grade** – Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, but rarely affects the extremities including hands and fingers; also difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs,

			standing up from a seated position, and/or reaching up. – If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation. – Consider, as necessary, discussing with the study physician. – Initial work-up should include clinical evaluation, creatine kinase, aldolase, LDH, BUN/creatinine, erythrocyte sedimentation rate or C-reactive protein level, urine myoglobin, and additional laboratory work-up as indicated, including a number of possible rheumatological/antibody tests (i.e., consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider Barium swallow for evaluation of dysphagia or dysphonia. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).
	Grade 1	• No dose modifications.	**For Grade 1** – Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated.

		– Consider Neurology consult. – Consider, as necessary, discussing with the study physician.
Grade 2	• Hold study drug/study regimen dose until resolution to Grade ≤1. • Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.	**For Grade 2** – Monitor symptoms daily and consider hospitalization. – Obtain Neurology consult, and initiate evaluation. – Consider, as necessary, discussing with the study physician. – If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant – If clinical course is *not* rapidly progressive, start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 2 to 3 days, continue additional work up and start treatment with IV methylprednisolone 2 to 4 mg/kg/day – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 2 to 3 days, consider starting another immunosuppressive therapy such as a TNF inhibitor (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.**
Grade 3 or 4	**For Grade 3** • Hold study drug/study regimen dose until resolution to Grade ≤1. • Permanently discontinue study	**For Grade 3 or 4** – Monitor symptoms closely; recommend hospitalization. – Obtain Neurology consult – Consider discussing with the study physician, as needed. – Promptly start IV methylprednisolone 2 to

	drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency. **For Grade 4** • Permanently discontinue study drug/study regimen.	4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 2 to 3 days, consider starting another immunosuppressive therapy such as a TNF inhibitor (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.** – Consider whether patient may require IV IG, plasmapheresis.

[a]ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Postow MD.
[b]FDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation.
[C]NCCN Clinical Practice Guidelines in Oncology "Management of Immunotherapy-Related Toxicities" Version 1.2020 – December 2019

AChE Acetylcholine esterase; ADL Activities of daily living; AE Adverse event; ALP Alkaline phosphatase test; ALT Alanine aminotransferase; AST Aspartate aminotransferase; BUN Blood urea nitrogen; CT Computed tomography; CTCAE Common Terminology Criteria for Adverse Events; ILD Interstitial lung disease; imAE immune-mediated adverse event; IG Immunoglobulin; IV Intravenous; GI Gastrointestinal; LFT Liver function tests; LLN Lower limit of normal; MRI Magnetic resonance imaging; NCI National Cancer Institute; NCCN National Comprehensive Cancer Network; PJP *Pneumocystis jirovecii* pneumonia (formerly known as *Pneumocystis carinii* pneumonia); PO By mouth; T3 Triiodothyronine; T4 Thyroxine; TB Total bilirubin; TNF Tumor necrosis factor; TSH Thyroid-stimulating hormone; ULN Upper limit of normal.

Other–Immune-Mediated Reactions

Severity Grade of the Event (NCI CTCAE v4.03)	Dose Modifications	Toxicity Management
Any Grade	Note: It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs, some of them are not noted specifically in these guidelines (e.g. immune thrombocytopenia, haemolytic anaemia, uveitis, vasculitis).	– The study physician may be contacted for immune-mediated reactions not listed in the "specific immune-mediated reactions" section – Thorough evaluation to rule out any alternative etiology (e.g., disease progression, concomitant medications, and infections) – Consultation with relevant specialist – Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Monitor as clinically indicated
Grade 2	• Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. • If toxicity worsens, then treat as Grade 3 or Grade 4. • Study drug/study regimen can be resumed once event stabilizes to Grade ≤1 after completion of steroid taper. • Consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper	**For Grade 2, 3, or 4** Treat accordingly, as per institutional standard, appropriate clinical practice guidelines, and other society guidelines (e.g., NCCN, ESMO)
Grade 3	Hold study drug/study regimen	
Grade 4	Permanently discontinue study drug/study regimen	

Note: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Study Physician."

AE Adverse event; CTCAE Common Terminology Criteria for Adverse Events; NCI National Cancer Institute.

Infusion-Related Reactions

Severity Grade of the Event (NCI CTCAE v4.03)	Dose Modifications	Toxicity Management
Any Grade	General Guidance	**For Any Grade** – Manage 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, or skin rashes) and anaphylaxis (e.g., generalized urticaria, angioedema, wheezing, hypotension, or tachycardia).
Grade 1 or 2	**For Grade 1** The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event. **For Grade 2** • The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event. • Subsequent infusions may be given at 50% of the initial infusion rate.	**For Grade 1 or 2** – 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. – Steroids should not be used for routine premedication of Grade ≤2 infusion reactions.
Grade 3 or 4	**For Grade 3 or 4** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Manage severe infusion-related reactions per institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and famotidine, and IV glucocorticoid).

CTCAE Common Terminology Criteria for Adverse Events; IM intramuscular; IV intravenous; NCI National Cancer Institute.

Non-Immune-Mediated Reactions

Severity Grade of the Event (NCI 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.
Grade 1	No dose modifications.	Treat accordingly, as per institutional standard.
Grade 2	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline.	Treat accordingly, as per institutional standard.
Grade 3	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. For AEs that downgrade to ≤Grade 2 within 7 days or resolve to ≤Grade 1 or baseline within 14 days, resume study drug/study regimen administration. Otherwise, discontinue study drug/study regimen.	Treat accordingly, as per institutional standard.
Grade 4	Discontinue study drug/study regimen (Note: For Grade 4 labs, decision to discontinue should be based on accompanying clinical signs/symptoms, the Investigator's clinical judgment, and consultation with the Sponsor.).	Treat accordingly, as per institutional standard.

Note: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Study Physician."

AE Adverse event; CTCAE Common Terminology Criteria for Adverse Events; NCI National Cancer Institute.

APPENDIX 2. Durvalumab DOSE VOLUME CALCULATIONS

For durvalumab flat dosing:

1. Cohort dose: X g

2. Dose to be added into infusion bag:

Dose (mL) = X g × 1000/50 (mg/mL)

where 50 mg/mL is durvalumab nominal concentration.

The corresponding volume of durvalumab should be rounded to the nearest tenth mL (0.1 mL).

3. The number of vials required for dose preparation is the next greatest whole number of vials from the following formula:

Number of vials = Dose (mL)/10.0 (mL/vial)

Example:

1. Cohort dose: 1.5 g

2. Dose to be added into infusion bag:

Dose (mL) = 1.5 g ×1000/50 (mg/mL) = 30.0 mL

3. The number of vials required for dose preparation:

Number of vials = 30.0 (mL)/10.0 (mL/vial) = 3 vials

APPENDIX 3. Tremelimumab DOSE VOLUME CALCULATIONS

For tremelimumab flat dosing:

1. Cohort dose: X mg

2. Dose to be added into infusion bag:

Dose (mL) = X mg/20 (mg/mL)

where 20 mg/mL is tremelimumab nominal concentration

The corresponding volume of tremelimumab should be rounded to the nearest tenth mL (0.1 mL).

3. The number of vials required for dose preparation is the next greatest whole number of vials from the following formula:

Number of vials = Dose (mL)/20 (mL/vial)

Example:

1. Cohort dose: 300 mg

2. Dose to be added into infusion bag:

Dose (mL) = 300 mg/20 (mg/mL) = 15 mL

3. The number of vials required for dose preparation:

Number of vials = 15 (mL)/20 (mL/vial) = 1 vial (containing 20ml) OR 12 vials (containing 1.25ml)