Clinical Study Protocol

Title Page

Clinical Study Protocol Title:	A Phase IIa, single-arm, multicenter study to investigate the clinical activity and safety of avelumab in combination with cetuximab plus gemcitabine and cisplatin in participants with advanced squamous non-small-cell lung cancer
Study Number:	MS201944-0170
Amendment Number:	1.0
Merck Compound Numbers:	Avelumab: MSB0010718C Cetuximab: EMD271786
Study Phase:	Phase IIa
Short Title:	Phase IIa Study of Avelumab and Cetuximab plus Gemcitabine and Cisplatin in Participants with squamous NSCLC
Coordinating Investigator:	PPD PPD
Sponsor Name and Legal Registered Address:	Merck KGaA Frankfurter Strasse 250 64293 Darmstadt, Germany Medical Responsible: Name: PPD Address: Merck KGaA Frankfurter Strasse 250 64293 Darmstadt, Germany Phone: PPD Mobile: PPD E-mail: PPD
Regulatory Agency Identifying Numbers:	EudraCT number: 2018-001529-24 ClinicalTrials.gov: NCT03717155
Protocol Version:	20 August 2019/Version 2.0
Replaces Version:	21 June 2018/Version 1.0
Approval Date:	20 August 2019

Medical Monitor Name and Contact Information:	PPD PPD PPD PPD PPD PPD Mobile: PPD Phone: PPD E-mail: PPD

Protocol Amendment Summary of Changes

Protocol History

Version Number	Type	Version Date
1.0	Original Protocol	21 June 2018
2.0	Global amendment 1.0	20 August 2019

Protocol Version 2.0 (20 August 2019)

This amendment is substantial based on the criteria in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The protocol is being amended based on the update of inclusion criterion number 1 regarding the upper age limit. In addition, switch to on-study anticancer therapy with carboplatin will be allowed for participants who cannot tolerate treatment with cisplatin. The other items are corrections to inconsistencies and clarifications.

Section # and Name	Description of Change	Brief Rationale
Title page	Amendment number added	Administrative update
Title page	Study Phase corrected	Administrative update
Title page	Information about the Regulatory Agency Identifying Numbers added	Administrative update
Title page	Protocol Version changed	Administrative update
Title page	Replaces Version added	Administrative update
Title page	Approval date added	Administrative update

Section # and Name	Description of Change	Brief Rationale
Title page	Details for the Medical Responsible and Medical Monitor updated	Administrative update
1.1 Synopsis Study Intervention Groups and Duration	Addition of the following text: Thereafter, avelumab and cetuximab…. disease progression **or unacceptable toxicity**. If cisplatin toxicity occurs, subjects may be switched to carboplatin treatment at the discretion of Investigator.	This change in criteria was to allow participants with cisplatin toxicity to remain in study by switching to carboplatin.
Table 1 Schedule of Activities	Replace the following wordings: From: Prior to the first 2 infusions… **at least** 1 hour…. of cetuximab. To: Prior to the first 2 infusions… **approximately** 1 hour…. of cetuximab. Addition of the following text: If cisplatin toxicity occurs, subjects may be switched to carboplatin at the discretion of the Investigator	To change the specification of timings for premedication for cetuximab. Alignment with Section 4.1 and criteria to allow participants with cisplatin toxicity to remain in the study.
Table 1 and Table 2 Schedule of Activities	Correction of tumor assessment interval for confirming CR or PR From: …no sooner than 4 weeks and no later than 6 weeks after the initial documentation of CR or PR. To: …no sooner **than 4 weeks after** the initial documentation of CR or PR. Replace the following wording: From: Prior to…... **at least** 1 hour prior to administration of cetuximab. To: Prior to…... **approximately** 1 hour prior to administration of cetuximab.	Alignment with Section 9.4.1.1 and per recommendation in RECIST v1.1.
Table 3 and Table 4 Schedule of Activities	Inclusion of the following information: From: within 2 hours prior to the study treatment infusion. To: within 2 hours prior to the **first** study intervention infusion.	Table 3 updated to clarify that certain samples have to be taken before any study intervention, i.e. gemcitabine /cisplatin are administered and alignment with Table 4.
Table 3 and Table 4 Schedule of Activities	Replace of the following information: From: 2 hours prior to the first study **treatment** infusion To: 2 hours prior to the first study **intervention** infusion	Editorial change to align with protocol wording.

Section # and Name	Description of Change	Brief Rationale
Table 4 Schedule of Activities	Replace the following wording: On visits 9 and 12, a further sample for **cetuximab** determination will be collected 3 hours after the end of avelumab infusion. With: "On visits 9 and 12, a further sample for **avelumab** determination will be collected 3 hours after the end of avelumab infusion".	Correction to reflect that PK samples for avelumab determination are taken and not for cetuximab.
2.2 Background	Addition of approval status for pembrolizumab in European Union added.	Per comment of the Istituto Superiore di Sanitá, Italy, the paragraph was updated to reflect the current approval status.
2.2 Background	Replace the following wording: "A European Medicines Agency marketing authorization application for this treatment regimen was withdrawn by the manufacturer in November 2017." With: "The European Medicines Agency **has granted a** marketing authorization application for this treatment regimen **in September 2018.**"	Administrative update.
2.2 Background	Information update Addition of the following text: Based on these results, this regimen received approval and marketing authorization in October 2018 by US FDA and in March 2019 by the European Commission.	Due to comments received from Istituto Superiore di Sanitá, Italy, this paragraph was also updated to reflect the current approval status as it has changed since the protocol was finalized.

Section # and Name	Description of Change	Brief Rationale
2.3 Benefit/Risk Assessment	Replace the following wording: **"Main risks** associated with cetuximab are:". With: **"Primary risks** associated with cetuximab are:".	Editorial change.
2.3 Benefit/Risk Assessment	Replace the following wording: From: The efficacy and safety of gemcitabine and cisplatin….; **this chemotherapy combination** …. is also reflected…. histological subtype. To: The efficacy and safety of gemcitabine and ~~cisplatin~~ **platinum-based doublet chemotherapy**……; ~~is~~ **the** combination **of gemcitabine and cisplatin** is also reflected…. histological subtype. However, toxicities such as renal impairment or ototoxicity prevent a number of patients from completion of the recommend cycles of therapy with cisplatin. Addition of the following text: For those patients unable to tolerate all required 4 cycles of cisplatin due to limiting toxicities, further continuation of a doublet regimen with a switch to carboplatin instead represents a viable option. Addition of following wording: From: For cisplatin, gemcitabine, the Summary of Product Characteristic……with the 2 compounds. To: For cisplatin, ~~and~~ gemcitabine, and **carboplatin** the Summary of Product Characteristics….. ~~2~~**3** compounds	Addition of benefit/risk for carboplatin was added.
4.1 Overall Design	Addition of the following text: At the discretion of the Investigator, a switch to carboplatin for the remainder of the platinum-doublet cycles (up to 4 cycles in total) will be allowed in subjects developing unacceptable toxicities to cisplatin. In these subjects, carboplatin at will be administered on Day 1 of each 3-week cycle at a dose of target area under the serum concentration-time curve of 5 (AUC 5) using the Calvert formula.	This change in criteria was to allow participants with cisplatin toxicity to remain in the study by switching to carboplatin.
5.1 Inclusion Criteria	Removed upper age limit of ≤ 69 years of age	To better reflect the age of the targeted patient population.
6.1 Study Intervention(s) Administration	Addition of the following column in Table 5: **Carboplatin (in case of cisplatin toxicities)**. In addition to that, information of Supplier/ Manufacturer details for cisplatin and **gemcitabine** column has also been updated. Replace the following text in Supplier/Manufacturer detail for cisplatin and gemcitabine: From: Cisplatin will be sourced from the local hospital pharmacy.	Supplier and manufacture detail for cisplatin and carboplatin addition.

Section # and Name	Description of Change	Brief Rationale
	Gemcitabine will be sourced from the local hospital pharmacy. To: Can be supplied locally by investigational site or centrally depending on local requirements and regulations. Addition of same text for Carboplatin for Supplier and manufacture. Addition of abbreviation AUC to the footnote	
6.2.3 Chemotherapy	Addition of the following text: From: For preparation and storage of gemcitabine and cisplatin……. the respective summary of product characteristics (SmPCs). To: For preparation and storage of gemcitabine and cisplatin **or carboplatin**, ……..the respective summary of product characteristics (SmPCs).	Addition of carboplatin
6.5.2 Permitted Medication	Addition of following text: For participants who develop unacceptable toxicities to cisplatin, chemotherapy treatment with carboplatin is allowed at the discretion of the Investigator.	This change in criteria was to allow participants with cisplatin toxicity to remain in the study by switching to carboplatin.
6.6.1 Sequencing and Continuation of Study Intervention Administration	Adding a time window: From …Treatment with the remainder of study interventions will not be delayed for a toxicity attributed to one of the compounds unless deemed necessary by the Investigator. Therefore, if there is a delay or a discontinuation for one of the drugs…. To: …Treatment with the remainder of study interventions will not be delayed **for more than 7 days** for a toxicity attributed to one of the compounds unless deemed necessary by the Investigator. Therefore, if there is a delay **of more than 7 days** or a discontinuation for one of the drugs…	Delay of study interventions due to toxicities related to chemotherapy needed as this is clinical practice for chemotherapy.
6.6.2 Avelumab	Addition of the following text: This regimen may be modified based on local treatment standards and guidelines including pretreatment modalities for chemotherapy as appropriate.	Alignment with wording used in schedule of assessments.
6.6.3 Cetuximab	Replace the following wording: From: Pretreatment with...is mandatory **at least** 1 hour before the first 2 cetuximab infusions. To: Pretreatment with...is mandatory **approximately** 1 hour before the first 2 cetuximab infusions.	Alignment with wording used in schedule of assessments.
6.6.4.1 Gemcitabine and Cisplatin	Inclusion of following information:	Editorial change to align with protocol wording.

Section # and Name	Description of Change	Brief Rationale
	From: After the starting dose, dose modifications (dose delays and dose changes) for toxicity… To: After the starting dose, dose modifications (dose delays and dose changes) for **chemotherapy-related** toxicity….	
Table 7	Addition of Table 7 Predosing Consideration for Carboplatin	Addition of table for recommended steps for adverse reaction observed in participants with carboplatin toxicity.
6.6.4.2 Carboplatin	Addition of the following text: For participants who must discontinue treatment with cisplatin due to unacceptable toxicities, continuation of platinum-based treatment (up to 4 cycles in total) with carboplatin is allowed at the discretion of the Investigator. For these subjects, carboplatin is administered intravenously at AUC 5 using the Calvert formula, over 30 to 60 minutes on Day 1 of each 3-week cycle. Participants receiving carboplatin should be monitored for myelosuppression with thrombopenia, leucopenia, neutropenia and anemia; infections; hepatic toxicity; renal toxicity; nausea and vomiting; ototoxicity; and peripheral neuropathies.	Addition of text for participants who switch to carboplatin due to cisplatin toxicity.
Table 8	Addition of Table for predosing consideration for carboplatin	Addition of predosing consideration for participants who switch to carboplatin.
Table 9 Dose Modification for Chemotherapy	Addition of dose modification for chemotherapy	Addition of dose modification column for carboplatin
6.8.1 Avelumab	Update of the following information: From 1 hour: As a routine precaution, participants enrolled in this study must be observed for 1-hour post avelumab infusion for the first 4 avelumab infusions, To: 2 hours: …As a routine precaution, participants enrolled in this study must be observed for 2 hours post avelumab infusion for the first 4 avelumab infusions…	Align the observation periods in the different protocol sections to reflect the 2 hours observation period after avelumab infusion.
6.8.3 Gemcitabine, Cisplatin and Carboplatin	Addition of the following text: Carboplatin Participants who switch to treatment with carboplatin after experiencing cisplatin-related toxicities should be monitored for symptoms of myelosuppression with thrombopenia, leucopenia, neutropenia and anemia; infections; nausea and vomiting; hepatic toxicity, renal toxicity, ototoxicity; and peripheral neuropathies as per SmPC recommendations. Premedication with anti-emetics and hydration are performed according to local standards.	Special precaution for participants on carboplatin
8.4 Treatment of Overdose	Inclusion of following information: From: Gemcitabine and Cisplatin	Addition of treatment of overdose for carboplatin

Section # and Name	Description of Change	Brief Rationale
	To: Gemcitabine and Cisplatin **or Carboplatin**:	
8.10 Immunogenicity Assessment	Correction of the following information: From: Samples will be collected prior to any cetuximab administration on the same Study Day. To: Samples will be collected prior to any **study intervention** administration on the same Study Day.	Alignment with schedule of assessments.
8.10 Immunogenicity Assessment	Correction of the following information: From: Samples will be collected prior to any avelumab administration on the same Study Day. To: Samples will be collected prior to any **study intervention** administration on the same Study Day.	Alignment with schedule of assessments.
9.4.2 Safety Analyses	Correction of the following information: From: …and 12-lead ECG, recorded at baseline and after administration of study treatment will be presented. To: …and 12-lead ECG, recorded at baseline and after **end** of study treatment will be presented.	Alignment with schedule of assessments.
9.4.3 Other Analyses	Moved the following sentence to PK subsection in the same section: Integrated analyses across studies, such as the population PK analysis will be presented separately from the main clinical study report (CSR).	PK subsection is more appropriate.
10 References	Removed: Paz-Ares LG, Luft A, Tafreshi A, et al. Phase 3 study of carboplatin-paclitaxel/nab-paclitaxel with or without pembrolizumab for patients with metastatic squamous non-small cell lung cancer. J Clin Oncol 36, 2018 (suppl; abstr 105). Added: Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. N Engl J Med 2018;379:2040-51.	Update due to updated in information in Section 2.2.
Appendix 1 Abbreviations	Added "CSR" = Clinical Study Report Added "AUC" = Area under concentration-time curve	Editorial change.
Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Replace the following wording: Main adverse reactions of cetuximab are skin reactions which may become severe, especially in combination with chemotherapy. The risk for secondary infections (mainly bacterial) is increased and cases of staphylococcal scalded skin syndrome, necrotising fasciitis and sepsis, in some cases with fatal outcome, have been reported.	Clarity to reflect that no adverse events of special interest are defined, and the known adverse drug reactions are listed.

Section # and Name	Description of Change	Brief Rationale
	With: "There are no specified AESI for cetuximab."	
Appendix 11 Sponsor Signature Page	Information added to the Regulatory Agency Identifying Numbers Clinical Study Protocol Version changed Details for the Medical Responsible updated	Administrative update.
Appendix 12 Coordinating Investigator Signature Page	Information added to the Regulatory Agency Identifying Numbers Clinical Study Protocol Version changed	Administrative update.
Appendix 13 Principal Investigator Signature Page	Information added to the Regulatory Agency Identifying Numbers Clinical Study Protocol Version changed	Administrative update.

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1 Protocol Summary

1.1 Synopsis

Protocol Title: A Phase IIa, single-arm, multicenter study to investigate the clinical activity and safety of avelumab in combination with cetuximab plus gemcitabine and cisplatin in participants with advanced squamous non-small-cell lung cancer (NSCLC).

Short Title: Phase IIa Study of Avelumab and Cetuximab plus Gemcitabine and Cisplatin in Participants with squamous NSCLC.

Rationale: The purpose of this study is to investigate the clinical activity and safety of avelumab in combination with cetuximab plus gemcitabine and cisplatin in participants with treatment-naïve advanced squamous NSCLC. Given that NSCLC represents a tumor type rich in expression of both programmed death ligand 1 (PD-L1) as well as epidermal growth factor receptor (EGFR), a combination of 2 compounds targeting both entities is compelling considering that EGFR expression is even higher in squamous NSCLC.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate efficacy by means of confirmed Best Overall Response (BOR) rate of the combination of cetuximab and avelumab plus doublet chemotherapy, defined as the proportion of participants having achieved confirmed complete response (CR) or partial response (PR) as BOR	• Confirmed BOR according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) assessed by Investigator
Secondary	
• To evaluate the safety and tolerability of the combination of cetuximab and avelumab plus doublet chemotherapy • To evaluate the progression-free survival (PFS) time • To assess the duration of response	• Occurrence of treatment-emergent adverse events (TEAEs) and treatment-related adverse events (AEs), treatment-related Grade ≥ 3 AEs, and immune-related AEs, according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE v5.0) • PFS time according to RECIST V1.1 by Investigator assessment • Duration of response (DOR) assessed from confirmed CR or PR until progression of disease (PD), death, or last tumor assessment
• To characterize pharmacokinetic (PK) profiles of avelumab and cetuximab when given in combination with chemotherapy	• Peak and trough avelumab and cetuximab serum concentration at pre-specified study visits
• To characterize the immunogenicity of the combination therapy with cetuximab and avelumab and chemotherapy	• Immunogenicity of cetuximab and of avelumab in combination therapy, as measured by separate antidrug antibody (ADA) assays
• To assess overall survival (OS)	• OS
CCI [redacted]	

Objectives	Endpoints
CCI [redacted]	[redacted]

Overall Design: A safety run-in part to evaluate the safety and tolerability of avelumab in combination with cetuximab plus gemcitabine and cisplatin is planned for the first 6 evaluable participants exposed. After each of the 6 participants has received the combination treatment for at least 3 weeks with no new safety concerns emerging after the Safety Monitoring Committee (SMC) evaluation and final decision, enrollment will be continued until a total of approximately 40 evaluable participants have been recruited.

Post-baseline tumor measurements to determine response will be performed every 9 weeks (starting Day 64/Week 10) for the first 6 months (until Week 28), and every 12 weeks thereafter. Adverse events will be assessed throughout the study period. Participant follow-up for progression and survival will continue until 12 months after the last participant receives the last dose.

Number of Participants: A sample size of 40 participants will be chosen for following reasons: The probability to observe 18 or more responders (confirmed CR or PR) out of 40 treated participants (45.0% response rate; 95% confidence interval [CI]: 29.3%, 61.5%) is 78.5% under the assumption of a true response rate of 50% (clinically relevant effect); whereas, if the true responder rate is 30% (a non-relevant effect regarding further development of this combination therapy in this indication), the probability to observe 18 or more responders is 3.2%.

Study Intervention Groups and Duration: Participants will receive all treatments for a total of four 3-week cycles. Thereafter, avelumab and cetuximab will be administered as maintenance treatment every 2 weeks until disease progression or unacceptable toxicity.

If cisplatin toxicity occurs, participants may be switched to carboplatin treatment at the discretion of Investigator.

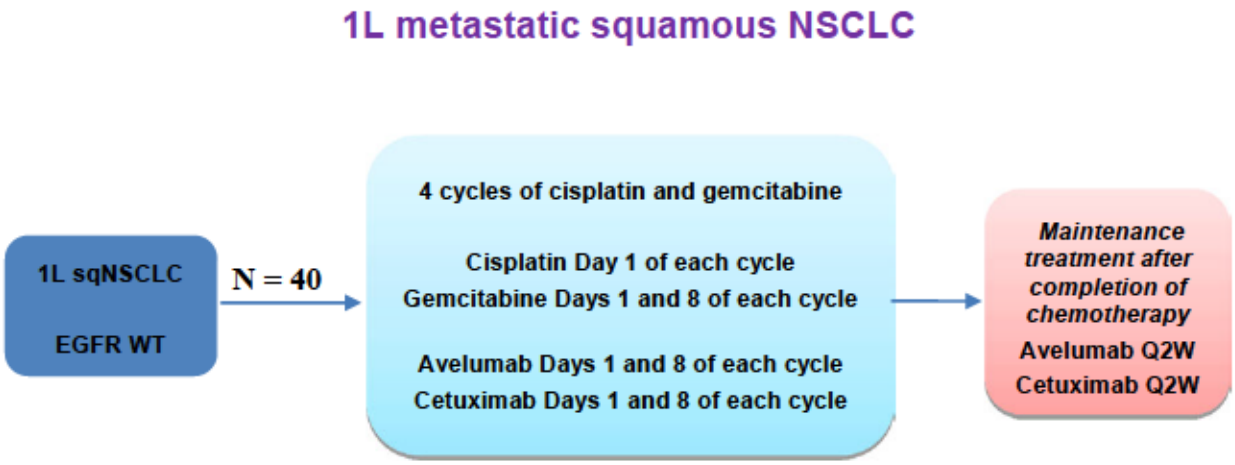
Involvement of Special Committee(s): SMC

A SMC, consisting of permanent members from the Sponsor and contract research organization (CRO), the Coordinating Investigator, and other optional members with expertise in the management of cancer subjects, will review the safety data on a regular basis throughout the trial. The SMC will decide by consensus and provide their recommendations on the continuation or

suspension of enrollment after an initial safety run-in of cetuximab in combination with avelumab plus gemcitabine and cisplatin and will review all available safety data. The specific working procedures will be described in an SMC charter, which will be established prior to the start of recruitment.

1.2 Schema

Figure 1 Overall Study Design Schema



1L = first-line; EGFR = epidermal growth factor receptor; Q2W = every 2 weeks; sqNSCLC = squamous non-small-cell lung cancer.

1.3 Schedule of Activities

Throughout the trial, the Screening window will be 28 days, followed by a treatment period and a safety follow-up period. A time window of up to 3 days before or 1 day after the scheduled visit day (-3/+1 days) will be permitted for all treatment procedures. The biweekly 14-day schedule in the maintenance phase after chemotherapy should be strictly adhered to, returning to the target date even if the previous visit was off schedule and outside of the described visit windows.

The 30-day Safety Follow-up Visit (± 5 days) and 90-day Safety Follow-up Phone Call (± 5 days) should be conducted, if possible, prior to the start of any new antineoplastic therapy. Participants without PD at End of Treatment (EoT) Visit will be followed up for tumor assessment until disease progression or start of subsequent anti-cancer therapy (whichever comes first).

In addition, participants in the follow-up period will be followed for survival (including assessment of any further tumor therapy).

Participant follow-up for progression and survival will continue until 12 months after the last participant received the last dose.

Re-initiation of avelumab is possible for participants who experience a CR, discontinue treatment, progress and later re-initiate treatment. The re-initiation should be performed as per the instructions in Section 6.6.

Table 1 Schedule of Activities (Avelumab/Cetuximab plus Chemotherapy)

Assessments & Procedures	Day -28 to Treatment Assignment	Treatment Period								Notes
		V1	V2	V3	V4	V5	V6	V7	V8	
		W1 D1	W2 D8	W4 D22	W5 D29	W7 D43	W8 D50	W10 D64	W11 D 71	
Written informed consent	X									
CCI										
Inclusion / exclusion criteria	X									
Medical history	X									
Disease history	X									
Demographic data	X									
CCI										
Physical examination	X	X	X	X		X		X	X	A full physical examination should be performed at Screening and the EoT visit. Physical examinations at all other visits should be directed to signs and symptoms. If Screening physical examination is done within 3 days of Visit 1 (Day 1), it does not have to be repeated at Visit 1.
Vital signs	X	X	X	X	X	X	X	X	X	
Height	X									
Weight	X	X	X	X	X	X	X	X	X	
ECOG PS	X	X		X		X		X	X	If the Day 1 ECOG PS was performed within 3 days prior to Day 1, it does not have to be repeated at Day 1 (unless the Investigator notices a decline that would exclude the participants from study participation).
12-lead ECG	X									
Concomitant medications and procedures	X	X	X	X	X	X	X	X	X	

Table 1 Schedule of Activities (Avelumab/Cetuximab plus Chemotherapy)

Assessments & Procedures	Day -28 to Treatment Assignment	Treatment Period								Notes
		V1	V2	V3	V4	V5	V6	V7	V8	
		W1 D1	W2 D8	W4 D22	W5 D29	W7 D43	W8 D50	W10 D64	W11 D 71	
AE collection and SAE collection	AEs are collected through the Safety Follow-up Visit. Treatment-related non-serious AEs are collected until the 90-day Safety Follow-up Phone Call. All SAEs are documented until the 90-day Safety Follow-up Phone Call, ongoing SAEs at the 90-day Safety Follow-up Visit will be followed up.									All participants will have an EoT visit within 7 days after the decision to discontinue study treatment. All AEs will be documented until the 30-day Safety Follow-up visit. After this visit, all SAEs and all treatment-related non-serious AEs need to be documented until the 90-day Safety Follow-up Phone Call. Participants with an ongoing SAE at the 90-day Safety Follow-up Phone Call must be monitored and followed by the Investigator until stabilization or until the outcome is known, unless the participant is documented as "lost to follow-up". At 90 days following the last treatment, participants will be contacted by the Investigator by telephone to collect information on new or ongoing SAEs and treatment-related non-serious AEs. Any SAE assessed by Investigator as related to study intervention must be reported whenever it occurs, irrespective of the time elapsed since the last administration of study intervention. Any participant who experienced related SAEs (as per Investigator) can be invited to the site for further evaluation at Investigator's discretion. If another antineoplastic therapy is administered before the end of the 30-day period, the 30-day Safety Follow-up visit should be conducted, if possible, prior to the start of this new therapy.
Hematology and hemostaseology	X	X	X	X	X	X	X	X	X	Complete blood count results must be available and reviewed prior to dose administration.
Full serum chemistry	X	X								Core serum chemistry results must be available and reviewed prior to dose administration.
Core serum chemistry			X	X	X	X	X	X	X	Core serum chemistry results must be available and reviewed prior to dose administration.
Urinalysis	X	X				X				A full urinalysis (dipstick plus microscopic evaluation) is required at Screening and at EoT visits and a basic urinalysis (dipstick only) every 6 weeks. If the basic urinalysis is abnormal, then a full urinalysis should be performed.

Table 1 Schedule of Activities (Avelumab/Cetuximab plus Chemotherapy)

Assessments & Procedures	Day -28 to Treatment Assignment	Treatment Period								Notes
		V1	V2	V3	V4	V5	V6	V7	V8	
		W1 D1	W2 D8	W4 D22	W5 D29	W7 D43	W8 D50	W10 D64	W11 D 71	
Pregnancy test	X	X			X			X		Follicle stimulating hormone at Screening, if applicable. β-HCG from serum at Screening and from urine thereafter for WOCBP. Results of the most recent pregnancy test should be available prior to the administration of study intervention.
HBV and HCV test	X									
T4 and TSH	X	X				X				
Whole blood for PGt	X									Whole blood sample will be collected before or on Day 1 for participants who provide PGt informed consent.
Mandatory tumor tissue (archived or screening / recent biopsy)	X									A recent biopsy (within 6 months prior to Screening) from a non-irradiated area should be collected at Screening. Samples can be provided as block or slides (blocks are preferable).
Tumor evaluation / staging (CT Scan / MRI / other established methods)	X							X		Post-Baseline Tumor assessments will be performed every 9 weeks (starting Day 64 / Week 10) for the first 6 months (until Week 28), then every 12 weeks thereafter. The tumor evaluation has a time window of 7 days prior to dosing (-7 days) and ± 7 days after the EoT visit. In case a tumor response (according to RECIST v1.1) is documented during the course of the study, confirmation of the response should be performed according to RECIST v1.1, preferably at the regularly scheduled 9-week assessment interval, but no sooner than 4 weeks after the initial documentation of CR or PR. Tumor evaluation at the EoT visit should only be performed if no disease progression has been documented previously. A CT scan or MRI should always be used (if MRI is used, CT of chest is mandatory). Participants without progressive disease at EoT visit will be followed up for disease progression (CT / MRI scans every 9 weeks, and after 6 months from treatment start, every 12 weeks) or start of subsequent anti-cancer therapy (whichever comes first).

Table 1 Schedule of Activities (Avelumab/Cetuximab plus Chemotherapy)

Assessments & Procedures	Day -28 to Treatment Assignment	Treatment Period								Notes
		V1	V2	V3	V4	V5	V6	V7	V8	
		W1 D1	W2 D8	W4 D22	W5 D29	W7 D43	W8 D50	W10 D64	W11 D 71	
										In addition, participants will be followed every 12 weeks for survival (including assessment of any further tumor therapy). The survival follow-up will continue until 1 year after the last participant receives the last dose of study drug. Under some circumstances, the participants may not be followed for 1 year for survival in this study, for example, the participants may be offered to enroll into a roll over study, or the Sponsor may terminate the study early.
Brain CT scan/MRI, bone scan/imaging	X									A brain CT / MRI scan is required before Day 1 if not performed within the previous 6 weeks, and beyond as clinically indicated. A bone scan (and/or any additional imaging needed to evaluate bone metastasis) should be done as clinically indicated. Bone metastases detected at Screening need to be followed at the tumor evaluation visits using similar imaging modality.
Dosing										
Pretreatment		X	X	X	X	X	X	X	X	Premedicate participants with an antihistamine and with paracetamol (acetaminophen) prior to the first 4 infusions of avelumab. Premedication should be administered for subsequent avelumab doses based upon clinical judgment and presence/severity of prior infusion reactions. Prior to the first 2 infusions, participants must receive premedication with an antihistamine and a corticosteroid approximately 1 hour prior to administration of cetuximab. This premedication is recommended prior to all subsequent infusions as well. On days where both avelumab and cetuximab are scheduled, administration of premedication solely prior to the cetuximab infusion, is acceptable. However, if the avelumab infusion is given more than 4 hours after the initial premedication, a new sequence of premedication has to be administered before the avelumab infusion. This regimen may be modified based on local treatment standards and guidelines including pretreatment modalities for chemotherapy as appropriate.

Table 1 Schedule of Activities (Avelumab/Cetuximab plus Chemotherapy)

Assessments & Procedures	Day -28 to Treatment Assignment	Treatment Period								Notes
		V1	V2	V3	V4	V5	V6	V7	V8	
		W1 D1	W2 D8	W4 D22	W5 D29	W7 D43	W8 D50	W10 D64	W11 D 71	
Cisplatin		X		X		X		X		Premedication and hydration for Cisplatin will be administered as described in Section 6.6.4 or according to local standards If cisplatin toxicity occurs, subjects may be switched to carboplatin at the discretion of the investigator
Gemcitabine		X	X	X	X	X	X	X	X	Premedication for Gemcitabine will be administered as described in Section 6.6.4 according to local standards
Avelumab		X	X	X	X	X	X	X	X	Participants receiving avelumab will remain on treatment until PD. Participants who have experienced initial disease progression may continue treatment with avelumab if the Investigator believes that the participant will experience clinical benefit from the treatment and there is no unacceptable toxicity resulting from the treatment. Participants receiving avelumab may continue as long as ECOG PS remains stable, and if in the opinion of the Investigator, the participant will benefit from continued treatment, and if there are no new symptoms or worsening of existing symptoms.
Cetuximab		X	X	X	X	X	X	X	X	Participants receiving cetuximab will remain on treatment until PD. On visits where both cetuximab and avelumab will be administered, cetuximab infusion will always be administered first followed by the avelumab infusion. Concurrent administration of both infusions is not permitted. Participants who have experienced initial disease progression may continue treatment with cetuximab if treatment with avelumab is also ongoing, and if the Investigator believes that the participant will experience clinical benefit from the treatment and there is no unacceptable toxicity resulting from the treatment. Participants receiving cetuximab may continue as long as ECOG PS remains stable, and if in the opinion of the Investigator, the participant will benefit from continued treatment, and if there are no new symptoms or worsening of existing symptoms.

AE = adverse event, B-HCG = β human chorionic gonadotropin, CR = complete response, CT = computed tomography, D = day, ECG = electrocardiogram, ECOG PS = Eastern Cooperative Oncology Group Performance Status, CCI [redacted], EoT = End of Treatment, HBV = hepatitis B virus, HCV = hepatitis C virus, MRI = magnetic resonance imaging, NSCLC = non-small cell lung cancer, PD = progression of disease, CCI [redacted], CCI [redacted], PR = partial response, RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1, SAE = serious adverse event, CCI [redacted], T4 = free thyroxine; TSH = thyroid stimulating hormone, V = visit, W = week, WOCBP = woman of childbearing potential.

Table 2 Schedule of Activities (Avelumab/Cetuximab Maintenance and Follow-up)

Assessments & Procedures	Treatment Period				Follow-Up			Notes
	V9	V10		EoT visit	Safety Visit		Long Term	
	W13 D 85	W15 D 99	Until PD	Within 7 Days of Decision to DC	30 (±5) days after Last Tx	Phone Call 90 (±5) days after Last Tx	Every 12 (±1) Weeks after Last Tx	
CCI [redacted]								
Physical examination	X	X	Q6W	X	X			A full physical examination should be performed at Screening and the EoT visit. Physical examinations at all other visits should be directed to signs and symptoms.
Vital signs	X	X	Q2W	X	X			
Weight	X	X	Q2W	X	X			
ECOG PS	X	X	Q2W	X	X			
12-lead ECG				X	X			
Concomitant medications and procedures	X	X	Q2W	X	X			
AE collection and SAE collection	AEs are collected through the Safety Follow-up Visit. Treatment-related non-serious AEs are collected until the 90-day Safety Follow-up Phone Call. All SAEs are documented until the 90-day Safety Follow-up Phone Call, ongoing SAEs at the 90-day Safety Follow-up Visit will be followed up.					X		All participants will have an EoT visit within 7 days after the decision to discontinue study treatment. All AEs will be documented until the 30-day Safety Follow-up visit. After this visit, all SAEs and all treatment-related non-serious AEs need to be documented until the 90-day Safety Follow-up Phone Call. Participants with an ongoing SAE at the 90-day Safety Follow-up Phone Call must be monitored and followed by the Investigator until stabilization or until the outcome is known, unless the participant is documented as "lost to follow-up". At 90 days following the last treatment, participants will be contacted by the Investigator by telephone to collect information on new or ongoing SAEs and treatment-related non-serious AEs. Any SAE assessed by Investigator as related to study intervention must be reported whenever it occurs, irrespective of the time elapsed since the last administration of study intervention. Any participant who experienced related SAEs (as per Investigator) can be invited to the site for further evaluation at Investigator's discretion.

Table 2 Schedule of Activities (Avelumab/Cetuximab Maintenance and Follow-up)

Assessments & Procedures	Treatment Period				Follow-Up			Notes
	V9	V10		EoT visit	Safety Visit		Long Term	
	W13 D 85	W15 D 99	Until PD	Within 7 Days of Decision to DC	30 (±5) days after Last Tx	Phone Call 90 (±5) days after Last Tx	Every 12 (±1) Weeks after Last Tx	
								If another antineoplastic therapy is administered before the end of the 30-day period, the 30-day Safety Follow-up Visit should be conducted, if possible, prior to the start of this new therapy.
Survival							X	Q12W, Assessment may be completed by phone
Hematology & hemostaseology	X	X	Q2W	X	X			Complete blood count results must be available and reviewed prior to dose administration.
Full serum chemistry				X	X			Core serum chemistry results must be available and reviewed prior to dose administration.
Core serum chemistry	X	X	Q2W					Core serum chemistry results must be available and reviewed prior to dose administration.
Urinalysis		X	Q6W	X				A full urinalysis (dipstick plus microscopic evaluation) is required at Screening and at EoT visits and a basic urinalysis (dipstick only) every 6 weeks. If the basic urinalysis is abnormal, then a full urinalysis should be performed.
Pregnancy test		X	Q4W		X			Follicle stimulating hormone at Screening, if applicable. β-HCG from serum at Screening and from urine thereafter for WOCBP. Results of the most recent pregnancy test should be available prior to the administration of study intervention.
T4 and TSH	X		Q6W		X			
Tumor evaluation / staging (CT Scan / MRI / other established methods)			Q9W for the first 6 months and Q12W thereafter	X			X	The tumor evaluation has a time window of 7 days prior to dosing (-7 days) and ± 7 days after the EoT visit but before start of any subsequent anti-cancer treatment. Post-Baseline Tumor assessments will be performed every 9 weeks (starting Day 64 / Week 10) for the first 6 months (until Week 28), then every 12 weeks thereafter. In case a tumor response (according to RECIST v1.1) is documented during the course of the study, confirmation of the response should be performed according to RECIST v1.1, preferably at the regularly scheduled 9-week assessment interval, but no sooner than 4 weeks after the initial documentation of CR or PR. Confirmation of PR can be confirmed at an assessment later than the next assessment after the initial documentation of PR. Tumor evaluation at the EoT visit should only be performed if no disease

Table 2 Schedule of Activities (Avelumab/Cetuximab Maintenance and Follow-up)

Assessments & Procedures	Treatment Period				Follow-Up			Notes
	V9	V10		EoT visit	Safety Visit		Long Term	
	W13 D 85	W15 D 99	Until PD	Within 7 Days of Decision to DC	30 (±5) days after Last Tx	Phone Call 90 (±5) days after Last Tx	Every 12 (±1) Weeks after Last Tx	
								progression has been documented previously. A CT scan or MRI should always be used (if MRI is used, CT of chest is mandatory). Participants without progressive disease at EoT visit will be followed up for disease progression (CT / MRI scans every 9 weeks, and after 6 months (after Week 28) from treatment start, every 12 weeks) or start of subsequent anti-cancer therapy (whichever comes first). In addition, participants will be followed every 12 weeks for survival (including assessment of any further tumor therapy). The survival follow-up will continue until 1 year after the last participant receives the last dose of study drug. Under some circumstances, the participants may not be followed for 1 year for survival in this study, for example, the participants may be offered to enroll into a roll over study, or the Sponsor may terminate the study early.
Dosing								Cisplatin and Gemcitabine will not be administered during the Maintenance Phase
Pretreatment	X	X	Q2W					Premedicate participants with an antihistamine and with paracetamol (acetaminophen) for subsequent avelumab doses based upon clinical judgment and presence/severity of prior infusion reactions. Prior to the first two infusions, participants must receive premedication with an antihistamine and a corticosteroid approximately 1 hour prior to administration of cetuximab. This premedication is recommended prior to all subsequent cetuximab infusions as well. On days where both avelumab and cetuximab are scheduled, administration of premedication solely prior to the cetuximab infusion, is acceptable. However, if the avelumab infusion is given more than 4 hours after the initial premedication, a new sequence of premedication has to be administered before the avelumab infusion. This regimen may be modified based on local treatment standards and guidelines including pretreatment modalities for chemotherapy as appropriate.
Avelumab	X	X	Q2W					Participants receiving avelumab will remain on treatment until PD. Participants who have experienced initial disease progression may continue

Table 2 Schedule of Activities (Avelumab/Cetuximab Maintenance and Follow-up)

Assessments & Procedures	Treatment Period				Follow-Up			Notes
	V9	V10		EoT visit	Safety Visit		Long Term	
	W13 D 85	W15 D 99	Until PD	Within 7 Days of Decision to DC	30 (±5) days after Last Tx	Phone Call 90 (±5) days after Last Tx	Every 12 (±1) Weeks after Last Tx	
								treatment with avelumab if the Investigator believes that the participant will experience clinical benefit from the treatment and there is no unacceptable toxicity resulting from the treatment. Participants receiving avelumab may continue as long as ECOG PS remains stable, and if in the opinion of the Investigator, the participant will benefit from continued treatment, and if there are no new symptoms or worsening of existing symptoms.
Cetuximab	X	X	Q2W					Cetuximab will be administered until PD. On visits where both cetuximab and avelumab will be administered, cetuximab infusion will always be administered first followed by the avelumab infusion. Concurrent administration of both infusions is not permitted. Participants who have experienced initial disease progression may continue treatment with cetuximab if treatment with avelumab is also ongoing, and if the Investigator believes that the participant will experience clinical benefit from the treatment and there is no unacceptable toxicity resulting from the treatment. Participants receiving cetuximab may continue as long as ECOG PS remains stable, and if in the opinion of the Investigator, the participant will benefit from continued treatment, and if there are no new symptoms or worsening of existing symptoms.

AE = adverse event, B-HCG = β human chorionic gonadotropin, CR = complete response, CT = computed tomography, D = day, DC = discontinuation, ECG = electrocardiogram, ECOG PS = Eastern Cooperative Oncology Group Performance Status, CCI [redacted], EoT = End of Treatment, MRI = magnetic resonance imaging, NSCLC = non-small cell lung cancer, PD = progression of disease, CCI [redacted], PR = partial response, CCI [redacted], Q2W = every 2 weeks, Q4W = every 4 weeks, Q6W = every 6 weeks, Q9W = every 9 weeks, Q12W = every 12 weeks, RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1, SAE = serious adverse event, CCI [redacted] T4 = free thyroxine; TSH = thyroid stimulating hormone, V = visit, W = week, WOCBP = woman of childbearing potential.

Table 3 Schedule of Activities – Pharmacokinetic, Antidrug Antibody, and CCI Sampling (Avelumab/Cetuximab plus Chemotherapy)

Assessments & Procedures	Day -28 to Treatment Assignment	Treatment Period								Notes
		V1	V2	V3	V4	V5	V6	V7	V8	
		W1 D1	W2 D8	W4 D22	W5 D29	W7 D43	W8 D50	W10 D64	W11 D 71	
CCI [redacted]										
Serum for Cetuximab PK		X	X	X	X	X	X	X	X	On visit 1 to 8, samples for cetuximab determination will be collected pre cetuximab dose, at end of cetuximab infusion, pre avelumab dose and at end of avelumab infusion. On visits 1, 2, 3, and 4, a further sample for cetuximab determination will be collected at the end of observation period (i.e. 2 hours after end of avelumab infusion). On visits 5, 6, 7, and 8, a further sample for cetuximab determination will be collected 30 minutes after the end of avelumab infusion. All samples are to be collected within 15 minutes of the scheduled time.
Serum for Cetuximab ADA		X								Samples for ADA to cetuximab determination will be collected within 2 hours prior to the first study intervention infusion
Serum for Avelumab PK		X	X	X	X	X	X	X	X	On visit 1 to 8, samples for Avelumab determination will be collected pre avelumab dose and at end of avelumab infusion. On visits 1, 2, 3, and 4, a further sample for avelumab determination will be collected at the end of observation period (i.e. 2 hours after end of avelumab infusion). On visits 5, 6, 7, and 8, a further sample for avelumab determination will be collected 30 minutes after the end of avelumab infusion. All samples are to be collected within 15 minutes of the scheduled time.

Table 3 Schedule of Activities – Pharmacokinetic, Antidrug Antibody, and [redacted] Sampling (Avelumab/Cetuximab plus Chemotherapy)

Assessments & Procedures	Day -28 to Treatment Assignment	Treatment Period								Notes
		V1	V2	V3	V4	V5	V6	V7	V8	
		W1 D1	W2 D8	W4 D22	W5 D29	W7 D43	W8 D50	W10 D64	W11 D 71	
Serum for Avelumab ADA		X		X		X		X		Samples for ADA to avelumab determination will be collected within 2 hours prior to the first study intervention infusion

ADA = antidrug antibody, ctDNA = circulating tumor deoxyribonucleic acid, D = day, mRNA = messenger ribonucleic acid, PK = Pharmacokinetics, V = visit, W = week.

Table 4 Schedule of Activities – Pharmacokinetic, Antidrug Antibody, and [redacted] Sampling (Avelumab/Cetuximab Maintenance and Follow-up)

Assessments & Procedures	Maintenance Phase						Follow-Up			Notes
	V9	V10	V11	V12		EoT visit	Safety Visit		Long Term	
	W13 D 85	W15 D 99	W17 D 113	W19 D 127	Until PD	Within 7 days of Decision to DC	30 (±5) days after Last Tx	Phone Call 90 (±5) days after Last Tx	Every 12 (±1) Weeks after Last Tx	
[redacted]										
Serum for Cetuximab PK	X	X	X	X	W25, W37, W49		X			Samples for cetuximab determination will be collected pre cetuximab dose, at end of cetuximab infusion, pre avelumab dose, and at end of avelumab infusion. On visits 9 and 12, a further sample for cetuximab determination will be collected 3 hours after the end of avelumab infusion. All samples are to be collected within 15 minutes of the scheduled time.
Serum for Cetuximab ADA							X			
Serum for Avelumab PK	X	X	X	X	W25, W37, W49	X	X			Samples for avelumab determination will be collected, pre avelumab dose, and at end of avelumab infusion.

Table 4 Schedule of Activities – Pharmacokinetic, Antidrug Antibody, and [redacted] Sampling (Avelumab/Cetuximab Maintenance and Follow-up)

Assessments & Procedures	Maintenance Phase						Follow-Up			Notes
	V9	V10	V11	V12		EoT visit	Safety Visit		Long Term	
	W13 D 85	W15 D 99	W17 D 113	W19 D 127	Until PD	Within 7 days of Decision to DC	30 (±5) days after Last Tx	Phone Call 90 (±5) days after Last Tx	Every 12 (±1) Weeks after Last Tx	
										On visits 9 and 12, a further sample for avelumab determination will be collected 3 hours after the end of avelumab infusion. All samples are to be collected within 15 minutes of the scheduled time.
Serum for Avelumab ADA	X		X		W25, W37, W49		X			Samples for ADA to avelumab determination will be collected within 2 hours prior to the first study intervention infusion.

ADA = antidrug antibody, ctDNA = circulating tumor deoxyribonucleic acid, D = day, DC = discontinuation, mRNA = messenger ribonucleic acid, PD = progression of disease, PK = Pharmacokinetics, V = visit, W = week.

2 Introduction

Avelumab is a novel, intravenously-administered programmed cell death ligand-1 (PD-L1) -blocking human antibody. Cetuximab is an anti-epidermal growth factor receptor (EGFR) chimeric monoclonal antibody that blocks the ligand binding site of the EGFR. The combination of avelumab and cetuximab, plus chemotherapy, is being developed for the treatment of patients with advanced squamous non-small cell lung cancer (NSCLC).

Complete information on the chemistry, pharmacology, efficacy and safety of avelumab and cetuximab is in the respective Investigator's Brochures and package inserts of the respective compounds.

CCI

[redacted]

2.2 Background

Metastatic NSCLC remains a challenging diagnosis with a need for new therapeutic approaches despite significant advances. Forty percent of patients with newly diagnosed NSCLC present with Stage IV disease. Treatment goals intend to prolong survival and control disease-related symptoms with current treatment options including cytotoxic chemotherapy and immune checkpoint inhibitors or targeted agents such as tyrosine kinase inhibitors in distinct subsets of patients.

Until recently, systemic therapeutic regimens in the first-line for patients with advanced NSCLC whose tumors do not harbor anaplastic lymphoma kinase (ALK) rearrangements or EGFR mutations were mainly chemotherapy with cisplatin or carboplatin-based doublets in patients who are eligible and can tolerate this treatment.

Besides platinum-based doublet regimens, the EGFR inhibitor necitumumab is approved as part of a combination regimen with gemcitabine and cisplatin for NSCLC with squamous histology. The results of the Phase III trial SQUIRE proved a survival benefit for patients treated with necitumumab plus cisplatin and gemcitabine compared to chemotherapy alone. Median overall survival for the triplet combination was 11.5 months vs 9.9 months (hazard ratio 0.84; 95% confidence interval [CI] 0.74–0.96; p = 0.01; Thatcher 2015).

In October 2016, the US Food and Drug Administration (FDA) and in January 2017, the European Commission, approved pembrolizumab (full approval) for the first-line treatment of patients with metastatic NSCLC whose tumors were high in PD-L1 expression (tumor proportion score > 50%), with no epidermal growth factor EGFR or ALK genomic tumor aberrations. The reported overall response rate reached 45% with a median progression-free survival (PFS) of 10.3 months. This treatment entered US National Comprehensive Cancer Network (NCCN) treatment guidelines and the 2018 European Society for Medical Oncology (ESMO) guidelines.

Moreover, combination therapies of immunotherapeutic agents and established chemotherapy regimen are being investigated to further improve response rates and survival in patients with advanced lung cancer since only a subset of patients respond to monotherapy with approved checkpoint inhibitors.

Accelerated approval was granted by the FDA in May 2017 for pembrolizumab in combination with pemetrexed and carboplatin for the treatment of patients with previously untreated metastatic non-squamous NSCLC based on an exploratory study. The study demonstrated an improvement in overall response rate and in progression-free survival for patients randomized to a cohort with pembrolizumab plus carboplatin and pemetrexed. The objective response rate (ORR) was 55% (95% CI: 42-68%, n = 60) for the pembrolizumab plus chemotherapy arm and 29% (95% CI: 18-41%, n = 63) for chemotherapy alone (Langer 2016); median PFS reached 13.0 months versus 8.9 months. The European Medicines Agency has granted a marketing authorization application for this treatment regimen in September 2018.

In addition, results of a Phase III study evaluating the efficacy of carboplatin-paclitaxel/nab-paclitaxel with or without pembrolizumab in untreated patients with metastatic squamous NSCLC were recently published (Paz-Ares 2018), reporting an overall response rate of 57.9% in the pembrolizumab+chemotherapy arm (N = 278) as compared to 38.4% in the chemotherapy arm (N = 281). A tolerable safety profile without any new safety concerns was observed for the pembrolizumab combination treatment. Based on these results, this regimen received approval and marketing authorization in October 2018 by the US FDA and in March 2019 by the European Commission.

Despite these promising advances, a high unmet medical need remains in the field of squamous advanced NSCLC given that only a part of patients benefits from the standard of care or newly approved treatment modalities with durable responses.

Avelumab

The immune checkpoint molecule PD-L1 and its receptor, programmed cell death protein-1 (PD-1), comprise an important immunosuppressive pathway implicated in tumor immune evasion. The PD-L1 is often upregulated in cancer and correlates with poor prognosis in some cancers (Chen 2016, Wang 2016). Avelumab (Bavencio®) is a human anti-PD-L1 immunoglobulin G1 monoclonal antibody developed by the Sponsor. Avelumab binds to PD-L1 and competitively blocks its interaction with PD-1. Blockade of the PD-L1/PD-1 pathway reverses T cell suppression within tumors, thereby promoting effective antitumor immune responses. Avelumab is also known to promote a Th1 response and stimulate IFNγ production. Finally, Avelumab has also been shown to induce antibody-dependent cell-mediated cytotoxicity in vitro (Boyerinas 2015).

Due to strong evidence supporting a major role for the PDL1/PD-1 pathway in tumor immune evasion, this pathway has become recognized as a highly promising target for therapeutic intervention (Blank 2006).

The combination of immunotherapies such as avelumab with other cancer therapies such as chemotherapy and targeted therapies may enhance the ability of the immune system, and prevent immune escape. Targeting multiple mechanisms by which tumor cells avoid elimination by the immune system may allow for synergistic effects and offer improved efficacy in broader patient populations.

Cetuximab

Cetuximab (Erbitux®) is an anti-EGFR monoclonal antibody that blocks the ligand binding site of the EGFR. The EGFR is a commonly expressed transmembrane glycoprotein of the tyrosine kinase growth factor receptor family. The EGFR gene, which is expressed in many normal human tissues, has been found to be a proto-oncogene; its activation results in the high expression of EGFR in many human tumor types. EGFR is richly expressed by a wide variety of solid tumors including NSCLC. EGFR is also known to mediate the resistance of cancer cells to radiation in a manner proportional to the degree of receptor expression. The prognostic significance of high levels of expression has emphasized the importance of EGFR as an anti-cancer drug target (Liang 2003, Huang 1999, Maurizi 1996).

Cetuximab blocks the binding of epidermal growth factor and other ligands to EGFR and prevents EGFR dimerization (Merck 2003), thereby inhibiting ligand induced activation of this receptor tyrosine kinase. This results in the inhibition of cell growth, induction of apoptosis, and decreased production of matrix metalloproteinase and vascular endothelial growth factor (Mendelsohn 1990). Cetuximab also stimulates EGFR internalization (Li 2005) and eventual degradation (Waksal 1999). In addition, cetuximab can mediate antibody-dependent cell-mediated cytotoxicity (Hadari 2004), a process dependent on both the affinity of cetuximab for the extracellular domain of EGFR and the level of cellular EGFR expression (Zhang 2006).

2.3 Benefit/Risk Assessment

The benefit/risk relationship has been carefully considered in the planning of the study. Based on the available nonclinical and clinical information to date, avelumab provides a positive benefit/risk status for advanced NSCLC, and the conduct of the trial is considered justifiable using the dose and dose regimen of avelumab and cetuximab as specified in this clinical study protocol (see Section 4.3). Clinical activity and safety of cetuximab in combination with platinum-based doublet chemotherapy was demonstrated by the FLEX trial (Pirker 2009). Moreover, efficacy and safety of combination therapies of an anti-PD-1 antibody with chemotherapy have been demonstrated in the frontline setting of NSCLC (Langer 2016).

Recent results of the SWOG0819 trial evaluating cetuximab plus carboplatin and paclitaxel with or without bevacizumab versus carboplatin and paclitaxel with or without bevacizumab in advanced NSCLC provided further evidence supporting the role of cetuximab in squamous cell NSCLC where patients with squamous cell histology who were EGFR FISH-positive had longer

overall survival with cetuximab treatment than those patients who did not receive cetuximab (Herbst 2018).

Furthermore, subgroup analyses of the SQUIRE trial which was conducted in a squamous cell NSCLC population treated with cisplatin and gemcitabine with or without necitumumab, showed an overall survival gain for patients whose tumors showed high EGFR expression in the necitumumab arm demonstrating efficacy and safety of an anti-EGFR antibody with a cisplatin/gemcitabine combination (Thatcher 2015). The benefit/risk profile of the combination of an anti-PD-1 antibody and an EGFR antibody was also shown to be safe in an NSCLC population based on the results published from an exploratory combination study of pembrolizumab and necitumumab (Besse 2017) where no new safety concerns were reported for the doublet combination.

The efficacy and safety of gemcitabine and platinum-based doublet chemotherapy in squamous NSCLC have already been widely demonstrated; the combination of gemcitabine and cisplatin is also reflected in the current ESMO guidelines as a recommended combination for lung tumors with squamous histological subtype. However, toxicities such as renal impairment or ototoxicity prevent a number of patients from completion of the recommend cycles of therapy with cisplatin.

For those patients unable to tolerate all required 4 cycles of cisplatin due to limiting toxicities, further continuation of a doublet regimen with a switch to carboplatin instead represents a viable option.

Specific risks associated with the use of avelumab and cetuximab as monoclonal antibodies have been observed.

Potentially overlapping risks observed with avelumab and cetuximab treatment are the following:

- Infusion-related reactions, including anaphylactic reactions
- Cutaneous reactions.

The primary risks of exposure to avelumab includes:

- Infusion-related reactions
- Immune-related adverse events (irAEs) (other than infusion-related reactions)

Primary risks associated with cetuximab are:

- Infusion-related reactions
- Cutaneous reactions.

Participants will be monitored closely for adverse events (AEs) observed throughout the study. Premedication regimen to minimize infusion-related reactions to avelumab and cetuximab has been determined previously. Premedication for cisplatin and gemcitabine will be administered according to local standards. Detailed treatment modification algorithms have been set up for the study interventions to provide guidance to Investigators for the handling of AEs.

Moreover, a Safety Run-in Period has been planned to allow for a detailed evaluation of the combination regimen by a Safety Monitoring Committee (SMC) before more participants are enrolled into the study.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of avelumab and cetuximab may be found in Section 4.2 (Scientific Rationale for Study Design) and the Investigator's Brochures.

For cisplatin, gemcitabine, and carboplatin the Summary of Product Characteristics provides more details on the AEs associated with the 3 compounds.

Based on the available nonclinical and clinical data to date, the conduct of the study, as specified in this protocol, is considered justifiable.

3 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate efficacy by means of confirmed Best Overall Response (BOR) rate of the combination of cetuximab and avelumab plus doublet chemotherapy, defined as the proportion of participants having achieved confirmed complete response (CR) or partial response (PR) as BOR	• Confirmed BOR according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) assessed by Investigator
Secondary	
• To evaluate the safety and tolerability of the combination of cetuximab and avelumab plus doublet chemotherapy • To evaluate the progression-free survival (PFS) time • To assess the duration of response	• Occurrence of treatment-emergent adverse events (TEAEs) and treatment-related adverse events (AEs), treatment-related Grade ≥ 3 AEs, and immune-related AEs, according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE v5.0) • PFS time according to RECIST v1.1 by Investigator assessment • Duration of response (DOR) assessed from confirmed CR or PR until progression of disease (PD), death, or last tumor assessment
• To characterize pharmacokinetic (PK) profiles of avelumab and cetuximab when given in combination with chemotherapy	• Peak and trough avelumab and cetuximab serum concentration at pre-specified study visits
• To characterize the immunogenicity of the combination therapy with cetuximab and avelumab and chemotherapy	• Immunogenicity of cetuximab and of avelumab in combination therapy, as measured by separate antidrug antibody (ADA) assays
• To assess overall survival (OS)	• OS
CCI [redacted]	

Objectives	Endpoints
CCI [redacted]	[redacted]

4 Study Design

4.1 Overall Design

This is a Phase IIa, single-arm, open-label, multicenter study to investigate the clinical activity and safety of avelumab in combination with cetuximab plus gemcitabine and cisplatin in participants who are treatment-naïve in the advanced NSCLC setting with squamous histology.

Approximately 40 evaluable participants are planned to be enrolled into the study. If the observed overall response rate in the population of 40 participants does not show a clinically meaningful magnitude of effect but subgroup analyses, for example, in EGFR H-score high participants, suggest a favorable effect, the study may be amended to include additional participants in order to corroborate the initial results.

A safety run-in part to evaluate the safety and tolerability of avelumab in combination with cetuximab plus gemcitabine and cisplatin is planned for the first 6 participants exposed.

Enrollment will only be allowed sequentially in groups, with the first group having only 1 participant treated until the end of the observation period followed by the second group with 2 additional participants treated until the end of the observational period, followed by third group with 3 additional participants treated until the end of the observational period. The observational period is 3 weeks that is 1 cycle.

After each of these initial groups of participants in the safety run-in part (n = 6 participants evaluable) have received the combination treatment for at least 3 weeks with no new safety concerns emerging for the combination after the SMC evaluation and final decision, enrollment will be continued in an unrestricted fashion until a total of approximately 40 participants evaluable for efficacy (full analysis set) have been recruited.

Participants are considered evaluable for safety assessment during the safety run-in if they have completed treatment with all study interventions as scheduled during the first cycle or have received at least 1 dose of any study intervention and were discontinued from at least 1 study intervention for toxicity. Participants who are not evaluable for safety or efficacy may be replaced except for participants enrolled during the safety run-in who fail evaluability due to safety issues.

Study treatment will be administered as follows:

Gemcitabine and cisplatin will be administered in 3-week cycles up to a maximum of 4 cycles of intravenous (iv) infusions until disease progression or unacceptable toxicities. Gemcitabine (1250 mg/m^2) is administered on Day 1 and Day 8 and cisplatin (75 mg/m^2) is administered on Day 1 of each 3-week cycle. At the discretion of the Investigator, a switch to carboplatin for the remainder of the platinum-doublet cycles (up to 4 cycles in total) will be allowed in subjects developing unacceptable toxicities to cisplatin. In these subjects, carboplatin will be administered on Day 1 of each 3-week cycle at a dose of target area under the serum concentration-time curve of 5 (AUC 5) using the Calvert formula.

- Avelumab (800 mg iv) will be administered on Day 1 and Day 8 of each 3-week cycle for the first 4 cycles along with concurrent chemotherapy as per schedule. Thereafter, avelumab will be given every 2 weeks in the Maintenance phase until disease progression or unacceptable toxicities.
- Cetuximab will be administered during the first 4 cycles of concurrent chemotherapy, with an iv dose of 250 mg/m^2 body surface area on Day 1 of each cycle and at a dose of 500 mg/m^2 body surface area on Day 8 of each cycle. Thereafter, cetuximab will be given every 2 weeks in the Maintenance phase, at the dose of 500 mg/m^2 iv until disease progression or unacceptable toxicities.

Tumor measurements to determine response will be performed every 9 weeks for the first 6 months, and every 12 weeks thereafter. Response to treatment will be evaluated by RECIST v1.1 (primary and secondary efficacy endpoints) and by irRECIST (other efficacy endpoints).

Adverse events will be assessed throughout the study period and evaluated using the NCI-CTCAE v 5.0.

Participant follow-up for progression and survival will continue until 12 months after the last participant received the last dose.

See Sections 1.2 (Schema), 1.3 (Schedule of Activities), 4.4 (End of Study Definition), and 6.7 (Study Intervention after the End of the Study) for additional details.

4.2 Scientific Rationale for Study Design

Beyond the documented clinical activity of both avelumab and cetuximab in advanced NSCLC, more recent data provide compelling scientific rationale to combine these 2 treatment modalities with chemotherapy particularly in NSCLC with squamous cell histology. The increased expression of EGFR (EGFR H-score $\geq$ 200) in squamous cell NSCLC tumors in a subset of patients who received cetuximab in combination with cisplatin and vinorelbine in the FLEX study (HR 0.62; 95% CI 0.43–0.88) was associated with improved survival outcomes in a post-hoc analysis (Pirker 2012). Furthermore, subgroup analyses of the SQUIRE trial which was conducted in a squamous cell NSCLC population treated with cisplatin and gemcitabine with or without necitumumab, showed an overall survival gain for patients whose tumors showed high EGFR expression in the necitumumab arm (hazard ratio 0.75; 95% CI 0.60 – 0.94) (Thatcher 2015).

Recent results of the SWOG0819 trial evaluating cetuximab plus carboplatin and paclitaxel with or without bevacizumab versus carboplatin and paclitaxel with or without bevacizumab in advanced NSCLC provided further evidence supporting the role of cetuximab in the treatment of squamous cell NSCLC. Although subgroup analyses showed that EGFR FISH-positivity was not predictive in the overall NSCLC patient population in the trial, patients with squamous cell histology who were EGFR FISH-positive had longer overall survival with cetuximab treatment than those patients who did not receive cetuximab (Herbst 2018). After the enrollment of 40 participants, subgroup analyses will be conducted in this trial as well for efficacy in tumors with, for example, PD-L1 expression, high EGFR expression and EGFR gene amplification. In case of promising efficacy results from an individual subset of patients, the study can be amended to include additional participants to substantiate the initial results.

The primary endpoint of confirmed BOR according to RECIST v1.1 as per Investigator assessment is being used as a direct early measure of antitumor activity in participants treated with the quadruplet combination. Confirmed BOR (confirmed CR or PR) is suitable for a single-arm early-phase study. The DOR, PFS, and OS times will also be determined and will serve to assess whether objective tumor response is associated with lasting clinical benefit or prolongs survival. The secondary endpoint of occurrence of TEAEs, treatment-related AEs, treatment-related Grade $\geq$ 3 AEs, and immune-related AEs according to the NCI-CTCAE v 5.0 during the defined observation period are being used as objective measures of safety.

A safety run-in of the first 6 enrolled participants with sequential treatment of individual participants is considered to be adequate to establish initial safety and tolerability given that the individual components as well as the combination of cetuximab with platinum-based chemotherapy have been tested in this population in different Phase II and III studies before, and given that the comparable combination of the EGFR antibody necitumumab and PD-1 antibody pembrolizumab had an acceptable safety profile in a Phase Ib study in NSCLC patients (Besse 2017).

Clinical efficacy of avelumab monotherapy was initially evaluated in a cohort of 156 subjects with treatment-naïve NSCLC who were treated with avelumab. At the time of the analyses, 26 subjects (16.7%) were still on study treatment, 130 subjects (83.3%) were off-treatment, 26 subjects (16.7%) were in follow-up, and 104 subjects (66.7%) had discontinued from the study.

Confirmed objective response according to RECIST 1.1 was observed for 31 subjects (19.9% [95% CI: 13.9, 27.0]). Three of 156 subjects (1.9%) had a CR and 28 subjects (17.9%) had a PR. The median DOR was 12.02 months (95% CI: 6.93, NE); the Kaplan-Meier estimate of 6-month durability of response was 70.7% (95% CI: 51.2, 83.6). Most responses occurred within the first 12 weeks of treatment (23 of 31 responses), with the onset of the first documented response corresponding to the first or second tumor assessment. The Kaplan-Meier estimated median OS time was 14.23 months (95% CI: 11.89, 17.18). Refer to the current version of the Investigator's Brochure for further details.

The most recently evaluated results of the Phase III study EMR100070-004 in 2L NSCLC comparing avelumab monotherapy to chemotherapy did not achieve its primary objective. However, the rate of patients in the chemotherapy control arm crossing over to immune checkpoint inhibitor therapy upon disease progression was 26.4%, which may have confounded the results.

Although not achieving its primary objective in improving overall survival in PD-L1 positive (> 1%) patients (HR: 0.90 [96% CI: 0.72–1.12], the results indicated nominal statistical significant improvements in overall survival versus the control arm in subgroups with moderate-to-high PD-L1 expression (50% or greater, which represented approximately 40% of the study population) and high PD-L1 expression population (PD-L1 expression 80% or greater, which represented approximately 30% of the study population) (HR: 0.67 [95% CI: 0.51–0.89], and HR 0.59 [95% CI: 0.42–0.83], respectively (Merck data on file).

A randomized controlled Phase III study of avelumab in first-line advanced NSCLC is currently ongoing.

4.3 Justification for Dose

Avelumab

A flat dose 800 mg of avelumab, iv, every 2 weeks was selected based on PK, target occupancy (TO), safety data, and population PK analysis and simulation. Avelumab has been studied at doses up to 20 mg/kg every 2 weeks, at which it was well tolerated, and maximum tolerated dose was not reached. To date, avelumab has been administered at the clinically active, safe, and tolerable dose of 10 mg/kg every 2 weeks to more than 1700 patients across multiple indications. Additionally, this dosing of avelumab has been approved for the treatment of Merkel cell carcinoma and urothelial carcinoma (UC), as well as used in ongoing studies for the treatment of NSCLC. Moreover, a weekly dosing regimen with 10 mg/kg of avelumab did not show any new safety concerns based on the analysis of overall 50 NSCLC patients treated for a period of at least 4 weeks. Avelumab was originally dosed on a mg/kg basis in order to reduce inter-subject variability in drug exposure. However, emerging data for mAbs, including the marketed PD-1 and PD-L1 immune checkpoint inhibitors nivolumab, pembrolizumab, and atezolizumab, reveal that body-weight based dosing regimens do not result in less variability in measures of exposure over fixed (ie, body-weight independent) dosing regimens (Wang 2009, Freshwater 2017, Zhao 2017). The same has been confirmed for avelumab through modeling and simulation. Additionally, flat dose regimen offers the advantages of less potential for dispensing errors, shorter dose preparation times in a clinical setting, and greater ease of administration.

Pharmacokinetic simulations suggest that exposures to avelumab across the available range of body weights are less variable with 800 mg every 2 weeks compared with 10 mg/kg every 2 weeks; exposures were similar near the population median weight. Low-weight subjects tended towards marginally lower exposures relative to the rest of the population when weight-based dosing was used, and marginally higher exposures when flat dosing was applied. However, the implications of these exposure differences are not expected to be clinically meaningful at any weight across the whole population. Furthermore, the 800 mg every 2 weeks dosing regimen is expected to result in C_{trough} > 1 mg/mL required to maintain avelumab serum concentrations at > 95% TO throughout the entire every 2 weeks dosing interval in all weight categories.

During the 4 chemotherapy cycles, administration of avelumab will be synchronized with the chemotherapy cycles, ie, dosing will be on Day 1 and Day 8 of each cycle. Exposures ($C_{max,ss}$ and AUC_{ss}) under this dose regimen of avelumab during the chemotherapy cycles are not expected to exceed those for previously administered regimens including 20 mg/kg every 2 weeks. A flat dose

of 800 mg every 2 weeks will be administered as a 1-hour iv infusion during the maintenance phase of this study.

Cetuximab

An initial loading dose of 400 mg/m^2 followed by subsequent weekly doses of 250 mg/m^2 is the dosing regimen included in the approved label.

Although currently approved only for weekly administration, several studies have evaluated once every 2 weeks administrations of cetuximab for treatment of mCRC, showing comparable safety and efficacy (Hubbard 2013). A population PK analysis showed no significant differences in tumor shrinkage or OS between the weekly and every 2 weeks regimens (Girard 2013). An every 2-week dose regimen allows a treatment synchronization with avelumab and with chemotherapies, reducing the burden to participants. Therefore, in this study, cetuximab administration will be synchronized with the chemotherapy cycles, ie, cetuximab will be administered with an iv dose of 250 mg/m^2 body surface area on Day 1 of each cycle and at a dose of 500 mg/m^2 body surface area on Day 8 of each cycle. Thereafter, during the maintenance phase, cetuximab will be synchronized with avelumab and administered once every 2 weeks at the maintenance dose of 500 mg/m^2 iv.

4.4 End of Study Definition

A participant has completed the study if he/she has completed all study parts, including the safety and survival follow-up as shown in Section 1.3 (Schedule of Activities).

The end of study is defined as 1 year after the last participant receives the last dose of protocol treatment. Once the primary and secondary objectives of this study have been analyzed, this study may be closed before the end of study definition has been met. Participants who are still on protocol treatment will be offered to receive further treatment on a roll-over protocol in case the study treatment or adequate alternative treatments, as judged by the Investigator, are not available to the participant.

5 Study Population

The criteria in Sections 5.1 (Inclusion Criteria) and 5.2 (Exclusion Criteria) are designed to enroll only participants who are appropriate for the study; thereby ensuring the study fulfills its objectives. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a participant is suitable for this study.

Prospective approval of protocol deviations to inclusion and exclusion criteria, also known as protocol waivers or exemptions, is not permitted.

Before performing any study assessments that are not part of the participant's routine medical care, the Investigator will confirm that the participant or the participant's legal representative has provided written informed consent, as indicated in Appendix 2 (Study Governance).

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

Age

1. Are 18 years or older, at the time of signing the informed consent

Type of Participant and Disease Characteristics

2. Histologically-confirmed Stage IV metastatic or recurrent (Stage IV) NSCLC of squamous histology as per the 7th International Association for the Study of Lung Cancer and the American Joint Committee on Cancer classifications.

3. Availability of formalin-fixed paraffin-embedded (FFPE) block containing tumor tissue or a minimum of 15 (preferably 25) unstained tumor slides (cut within 1 week) suitable for PD-L1 expression and EGFR expression/amplification assessments, from a recently obtained (within 6 months) biopsy or a fresh baseline tumor biopsy collected from a non-irradiated area.

4. At least 1 measurable lesion per RECIST v1.1 criteria. A lesion that has been irradiated can be used as a measurable lesion providing that disease has progressed at that site

5. Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 to 1 at study entry.

6. Adequate hematological function defined by white blood cell (WBC) count $\geq 2.5 \times 10^9$/L with absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L, lymphocyte count $\geq 0.5 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, and hemoglobin ≥ 9 g/dL (may have been transfused).

7. Adequate hepatic function defined by a total bilirubin level $\leq 1.5 \times$ the upper limit of normal (ULN) range and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels $\leq 2.5 \times$ ULN except for participants with documented metastatic disease to the liver for whom AST and ALT levels $\leq 5 \times$ ULN are acceptable. Patients with documented Gilbert disease are allowed if total bilirubin is less than $3 \times$ ULN.

8. Adequate renal function defined by an estimated creatinine clearance > 60 mL/minute according to the Cockcroft-Gault formula or by 24-hour urine collection for creatinine clearance or according to local institutional standard method.

9. Estimated life expectancy of at least 3 months.

Sex

10. Are male or female.

- A male participant must agree to use and to have their female partners use a highly effective contraception (ie, methods with a failure rate of less than 1% per year) as detailed in Appendix 3 of this protocol 30 days before the first dose of study intervention (as appropriate), during the study intervention period and for at least 60 days after the last dose of study intervention and refrain from donating sperm during this period.
- A female is eligible if she is not pregnant (ie, after a confirmed menstrual period and a negative serum pregnancy test), not breastfeeding, and at least one of the following conditions applies:

    a. Is **not** a woman of childbearing potential (WOCBP), as defined in Appendix 3

OR

b. Is a WOCBP who agrees to use a highly effective contraceptive method (ie, has a failure rate of less than 1% per year), as listed in Appendix 3, 30 days before the start of the first dose of study intervention (as appropriate), during the study intervention period and for at least 60 days after the last dose of study intervention.

Informed Consent

11. Can give signed informed consent, as indicated in Appendix 2 (Study Governance), which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and this protocol.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Participants whose tumor disease harbors an activating EGFR mutation or ALK rearrangement. Participants with tumors of unknown EGFR or ALK status will require testing only in never smokers.

2. All participants with brain metastases, except those meeting the following criteria:

   a. Brain metastases that have been treated locally and are clinically stable for at least 4 weeks prior to treatment start.

   b. No ongoing neurological symptoms that are related to the brain localization of the disease (sequelae that are a consequence of the treatment of the brain metastases are acceptable).

   c. Participants must be either off steroids or on a stable or decreasing dose of < 10mg daily prednisone (or equivalent).

3. Previous malignant disease (other than NSCLC) within the last 5 years (except adequately treated non-melanoma skin cancers, carcinoma in situ of skin, bladder, cervix, colon/rectum, breast, or prostate) unless a complete remission without further recurrence was achieved at least 2 years prior to study entry and the participant was deemed to have been cured with no additional therapy required or anticipated to be required.

4. Active infection requiring systemic therapy.

5. Known history of human immunodeficiency virus or known acquired immunodeficiency syndrome.

6. Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection at Screening (positive HBV surface antigen or HCV ribonucleic acid (RNA) if anti-HCV antibody screening test positive).

7. Active autoimmune disease that might deteriorate when receiving an immunostimulatory agent:

    a. Participants with diabetes type I, vitiligo, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible.

    b. Administration of steroids through a route known to result in a minimal systemic exposure (topical, intranasal, intro-ocular, or inhalation) are acceptable.

8. Interstitial parenchymal lung disease.

9. Pregnancy or lactation.

10. Known alcohol or drug abuse as determined by the Investigator.

11. History of uncontrolled intercurrent illness including but not limited to:

    a. Hypertension uncontrolled by standard therapies (not stabilized to 150/90 mmHg or lower)

    b. Uncontrolled active infection.

    c. Uncontrolled diabetes (for example, hemoglobin A1c $\geq$ 8%).

12. Clinically significant (ie, active) cardiovascular disease: cerebral vascular accident/stroke (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), unstable angina, congestive heart failure ($\geq$ New York Heart Association Classification Class II), or serious cardiac arrhythmia requiring medication.

13. Known history of inflammatory colitis, inflammatory bowel disease, pneumonitis, pulmonary fibrosis.

14. Any psychiatric condition that would prohibit the understanding or rendering of informed consent or that would limit compliance with study requirements.

Prior/Concomitant Therapy

15. Prior systemic therapy for metastatic NSCLC.

16. Prior therapy with any antibody/drug targeting T-cell coregulatory proteins (immune checkpoints) such as anti-programmed death 1 (PD-1), anti-PDL1, anti-PD-L2, anti-cytotoxic T lymphocyte antigen-4 (CTLA-4), anti-TIM3, anti-LAG3, anti-TIGIT or other antibodies.

17. Concurrent anti-cancer treatment (for example, cyto-reductive therapy, radiotherapy [with the exception of palliative radiotherapy], immune therapy, or cytokine therapy, except for erythropoietin) within the previous 28 days from start of treatment.

18. Prior chest irradiation within 2 weeks before study entry.

19. Major surgery for any reason, except diagnostic biopsy, within 4 weeks of the study treatment and/or if the participant has not fully recovered from the surgery within 4 weeks of the study treatment.

20. Current use of the following medications at the time of enrollment:

    a. Immunotherapy or immunosuppressive drugs (for example, chemotherapy or systemic corticosteroids) EXCEPT for the following: a. intranasal, inhaled, topical steroids, or local steroid injection (for example, intra-articular injection); b. systemic corticosteroids at physiologic doses ≤ 10 mg/day of prednisone or equivalent; c. steroids as premedication for hypersensitivity reactions (for example, computed tomography [CT] scan premedication).

    b. Growth factors EXCEPT for granulocyte-colony stimulating factor (G-CSF), erythropoietin and darbepoietin alpha.

    c. Herbal remedies with immunostimulating properties (for example, mistletoe extract) or known to potentially interfere with major organ function (for example, hypericin).

21. Prior organ transplantation, including allogeneic stem cell transplantation.

22. Known prior severe hypersensitivity to the study interventions or any component in its formulations, including known severe hypersensitivity reactions to monoclonal antibodies (NCI-CTCAE v5.0 Grade ≥ 3) and other acute and chronic medical conditions including any history of anaphylaxis, or uncontrolled asthma.

23. Persisting toxicity related to prior therapy of Grade > 1 NCI-CTCAE v5.0 (except neuropathy and alopecia) however, alopecia, sensory neuropathy Grade ≤ 2, or other Grade ≤ 2 AEs not constituting a safety risk based on Investigator's judgment are acceptable.

24. Administration of a live vaccine 30 days before the start of study treatment.

Prior/Concurrent Clinical Study Experience

25. Use of any investigational drug within 28 days before the start of study treatment.

Diagnostic Assessments

Not applicable.

Other Exclusions

26. Legal incapacity or limited legal capacity.

5.3 Lifestyle Considerations

No specific lifestyle or dietary restrictions are required throughout the study.

5.3.1 Meals and Dietary Restrictions

No food and drink restrictions have to be considered before or after the study intervention.

5.3.2 Caffeine, Alcohol, and Tobacco

No restrictions on caffeine, alcohol or tobacco use are required during the study.

5.3.3 Activity

Scheduled 12-lead electrocardiograms (ECGs) will be recorded after the participant has been in a supine position breathing quietly for 5 minutes. For blood pressure and heart rate, participants will also need to rest for 5 minutes before measurements are taken. The ECG will be repeated at any other scheduled or unscheduled visit only if it is clinically warranted in the opinion of the Investigator.

5.4 Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened for hematology and chemistry parameters.

6 Study Intervention(s)

Study intervention is any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant per the study protocol.

6.1 Study Intervention(s) Administration

Table 5 Study intervention(s) details

Study Intervention Name:	Cisplatin	Carboplatin (in case of cisplatin toxicities)	Gemcitabine	Avelumab	Cetuximab
Unit Dose Strength(s)/ Dosage Level(s):	75 mg/m^2	AUC 5	1250 mg/m^2	800 mg	250 mg/m^2 on Day 1 and 500 mg/m^2 on Day 8 of the first 4 cycles of concurrent chemotherapy; 500 mg/m^2 during the Maintenance phase
Route of Administration	Iv				
Dosing Instructions	See Section 6.6				

Study Intervention Name:	Cisplatin	Carboplatin (in case of cisplatin toxicities)	Gemcitabine	Avelumab	Cetuximab
Supplier/ Manufacturer	Can be supplied locally by investigational site or centrally depending on local requirements and regulations	Can be supplied locally by investigational site or centrally depending on local requirements and regulations	Can be supplied locally by investigational site or centrally depending on local requirements and regulations.	Avelumab will be supplied by the Sponsor and packaged, labeled, and distributed for clinical studies by a suitable service provider and finally released by a Sponsor qualified person under Good Manufacturing Practice conditions.	Cetuximab will be supplied by the Sponsor and packaged, labeled, and distributed for clinical studies by a suitable service provider and finally released by a Sponsor qualified person under Good Manufacturing Practice conditions.
Packaging and Labeling				Avelumab is formulated as a 20 mg/mL solution and is supplied by the Sponsor in single-use glass vials, stoppered with a rubber septum and sealed with an aluminum flip-off seal. Each vial will be packaged and labeled per all applicable regulatory requirements and Good Manufacturing Practice Guidelines. The information on the label will be in accordance with approved submission documents.	Cetuximab is formulated as a 5 mg/mL solution and is supplied by the Sponsor in in single-use glass vials, closed with a rubber stopper and sealed with an aluminum flip-off seal. Each vial will be packaged and labeled per all applicable regulatory requirements and Good Manufacturing Practice Guidelines. The information on the label will be in accordance with approved submission documents.

Study Intervention Name:	Cisplatin	Carboplatin (in case of cisplatin toxicities)	Gemcitabine	Avelumab	Cetuximab
				Additional details of packaging and labelling of the IMP will be defined in the separate Manual of Procedure.	Additional details of packaging and labelling of the IMP will be defined in the separate Manual of Procedure.
AUC = Area under the concentration-time curve					

6.1.1 Packaging and Labeling of Study Intervention

Study intervention will be packaged and labeled in accordance with all applicable regulatory requirements and Good Manufacturing Practice guidelines. The information on the label will be in accordance with approved submission documents.

Study intervention will be shipped in suitable transport containers according to its storage and shipping conditions. Shipments are monitored with temperature control devices.

6.2 Study Intervention(s) Preparation, Handling, Storage, and Accountability

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

- Upon receipt of the study intervention(s), the Investigator or designee must confirm appropriate temperature conditions have been maintained during transit and any discrepancies are reported and resolved before use. Also, the responsible person will check for accurate delivery and acknowledge receipt by signing or initialing and dating the appropriate document and returning it to the location specified. A copy will be archived for the Investigator Site File.
- Only participants enrolled in the study may receive study intervention(s) and only authorized site staff may supply or administer it. All study intervention(s) must be stored in a secure, environmentally-controlled, and monitored (manual or automated) area, in accordance with the labeled storage conditions, and with access limited to the Investigator and authorized site staff.
- Dispensing will be recorded on the appropriate accountability forms so that accurate records will be available for verification at each monitoring visit.
- Study intervention(s) accountability records at the study site will include the following:
  - Confirmation of receipt, in good condition and in the defined temperature range.
  - The inventory provided for the clinical study and prepared at the site.
  - The dose(s) each participant used during the study.

- The disposition (including return, if applicable) of any unused study intervention(s).
- Dates, quantities, batch numbers, vial numbers, expiry dates, formulation (for study interventions prepared at the site), and the participant numbers.

- The Investigator site will maintain records, which adequately documents that participants were provided the doses specified in this protocol, and all study intervention(s) provided were fully reconciled.
- Unused study intervention(s) must not be discarded or used for any purpose other than the present study. No study intervention that is dispensed to a participant may be re-dispensed to a different participant.
- A Study Monitor will periodically collect the study intervention(s) accountability forms.
- Further guidance and information for the final disposition of unused study intervention(s) are provided in the Study Reference Manual.

6.2.1 Avelumab

CCI [redacted]

6.2.2 Cetuximab

CCI [redacted]

CCI [redacted]

6.2.3 Chemotherapy

For preparation and storage of gemcitabine and cisplatin or carboplatin, please consult the local prescribing information or the respective summary of product characteristics (SmPCs).

6.3 Measures to Minimize Bias: Study Intervention Assignment and Blinding

6.3.1 Study Intervention Assignment

An Interactive Voice Response System will be employed to assign study intervention to participants and facilitate resupply of study intervention at study sites.

6.3.2 Blinding

Not applicable.

6.4 Study Intervention Compliance

In this study, participants will receive study intervention at the investigational site. Well-trained medical staff will monitor and perform the study drug administration. The information of each study drug administration including the date, time, and dose of study drug will be recorded on the electronic case report form (eCRF). The Investigator will make sure that the information entered into the eCRF regarding drug administration is accurate for each participant. Any reason for noncompliance should be documented.

Noncompliance is defined as a participant missing > 1 cycle of trial treatment for nonmedical reasons and barring any extenuating circumstances in the opinion of the Investigator. If 1 cycle

was missed and the interval between the subsequent treatment cycle and the last administered treatment cycle is longer than 4 weeks for nonmedical reasons, the criteria of insufficient compliance are met as well. Continuation of treatment should be discussed with the Medical Monitor under consideration of potential benefits and risks of study interventions and any alternative options.

6.5 Concomitant Therapy

6.5.1 Rescue Medicine

Immediate access to an Intensive Care Unit or equivalent environment and appropriate medical therapy (including epinephrine, corticosteroids, iv antihistamines, bronchodilators, and oxygen) must be available for use in the treatment of infusion-related reactions.

If hypersensitivity reaction occurs, the participant must be treated according to the best available medical practice. Participants should be instructed to report any delayed reactions to the Investigator immediately. In addition, all hypersensitivity reactions are to be reported in a timely manner.

6.5.2 Permitted Medicines

- Any medications, therapies, or procedures (other than those excluded by the clinical study protocol) that are considered necessary for the participants' welfare and will not interfere with the study medication may be given at the Investigator's discretion.
- Other drugs to be used for prophylaxis, treatment of hypersensitivity reactions, and treatment of fever or flu-like symptoms are permitted.
- Prophylactic or rescue medications may be administered due to anticipated or observed adverse reactions or emergency situations.
- For participants who develop unacceptable toxicities to cisplatin, a switch to chemotherapy treatment with carboplatin is allowed at the discretion of the Investigator.

The only permitted corticosteroids and growth factors are the following:

- Intranasal, inhaled, topical steroids, or local steroid injection (for example, intra-articular injection).
- Systemic corticosteroids at physiologic doses $\leq$ 10 mg/day of prednisone or equivalent.
- Steroids as premedication for hypersensitivity reactions (for example, premedication prior to cetuximab administration or CT scans).
- Erythropoietin, darbepoietin alpha, and G-CSF.

Any medicines that are considered necessary to protect the participant's welfare in emergencies may be given at the Investigator's discretion, regardless if it results in a protocol deviation.

6.5.3 Prohibited Medicines

- Prior systemic therapy for metastatic NSCLC.
- Prior therapy with any antibody/drug targeting T-cell coregulatory proteins (immune checkpoints) such as anti-programmed death 1 (PD-1), anti-PDL1, anti-PD-L2, anti-cytotoxic T lymphocyte antigen-4 (CTLA-4), anti-TIM3, anti-LAG3, anti-TIGIT or other antibodies.
- Prior chest irradiation within 2 weeks before study entry.
- Immunotherapy, immunosuppressive drugs (ie, chemotherapy not specified in the protocol or systemic corticosteroids except for those specified in Section 6.5.2).
- Growth factors, for exceptions see Section 6.5.2.
- Administration of a live vaccine within 30 days of study treatment.
- Herbal remedies with immunostimulating properties (for example, mistletoe extract) or known to potentially interfere with major organ function (for example, hypericin).
- Concurrent anti-cancer treatment (for example, cyto-reductive therapy, non-palliative radiotherapy, immune therapy, or cytokine therapy except for the study interventions) within the previous 28 days from start of treatment or during study treatment.

Use of a prohibited concomitant drug will result in withdrawal from study treatment, where the predefined consequence is treatment withdrawal if considered necessary by the Investigator or the Sponsor.

6.5.4 Other Interventions

Permitted

- Palliative short course, limited field (ie, ≤ 10 fractions and ≤ 30% bone marrow involvement or per institutional standard) bone-directed radiotherapy may be administered during the study. The assessment of PD will be made according to RECIST v1.1 (Eisenhauer 2009) and not based on the necessity for radiotherapy.

Prohibited

The following nondrug therapies must not be administered during the study (and within 28 days before the start of study treatment):

- Surgery to any tumor lesion for symptom management or tumor control is not permitted during the study treatment except as described in Section 6.6.5. For any other surgical interventions planned during the study, study treatment should be delayed to allow participant's recovery, for up to a maximum of 4 weeks.
- Radiotherapy with the exception of palliative radiotherapy if considered medically necessary by the Investigator for participants with confirmed PD.

Record in the case report form (CRF) all concomitant therapies (for example, medicines or nondrug interactions) used from the time the participant signs the informed consent until

completion of the study, including any changes. For prescription and over-the-counter medicines, vaccines, vitamins, and herbal supplements, record the name, reason for use, dates administered, and dosing information.

Use of a prohibited intervention will result in withdrawal from study treatment, where the predefined consequence is treatment withdrawal if considered necessary by the Investigator or the Sponsor (See Section 7).

Contact the Medical Monitor for any questions on concomitant or prior therapy.

6.6 Dose Selection and Modification

6.6.1 Sequencing and Continuation of Study Intervention Administration

On administration visits, chemotherapy administration will be initiated first, followed by infusion of the antibodies cetuximab and finally avelumab. Co-administration of avelumab and cetuximab or chemotherapy at the same time is not allowed.

Avelumab infusions should not start earlier than 1 hour after the completion of cetuximab infusions.

On days where both avelumab and cetuximab are scheduled, administration of premedication solely prior to the cetuximab infusion, is acceptable. However, if the avelumab infusion is given more than 4 hours after the initial premedication, a new sequence of premedication has to be administered before the avelumab infusion.

Treatment with the remainder of study interventions will not be delayed for more than 7 days for a toxicity attributed to one of the compounds unless deemed necessary by the Investigator. Therefore, if there is a delay of more than 7 days or a discontinuation for one of the drugs, the participant will continue to receive scheduled infusions of the other drugs and the other IMPs may be continued up to until either PD, as assessed by the Investigator, unacceptable toxicity, or other withdrawal criteria apply. Participants will continue to receive scheduled evaluation visits until PD, as assessed by the Investigator.

6.6.2 Avelumab

Participants will receive avelumab as an iv infusion at a fixed dose of 800 mg over a duration of 1 hour (- 10 minutes, ie, over 50 to 60 minutes) on Day 1 and Day 8 of each 3-week chemotherapy cycle. After completion of chemotherapy, avelumab will be administered once every 2 weeks. Apart from a change from a body-weight based dose to a fixed dose, relative to earlier studies, this study will follow standard procedures for the administration of avelumab. In order to mitigate infusion-related reactions, mandatory premedication with antihistamine and paracetamol (acetaminophen) for the first 4 doses is required. This regimen may be modified based on local treatment standards and guidelines including pretreatment modalities for chemotherapy as appropriate. Premedication should be administered for subsequent avelumab doses based upon clinical judgment and presence/severity of prior infusion reactions. Modifications of the infusion

rate due to infusion-related reactions, as well as for other reasons, are described in Section 6.9 (Management of Adverse Events of Interest). There will be no dose reductions for avelumab.

6.6.3 Cetuximab

Cetuximab will always be administered before avelumab on treatment days where both agents are planned to be administered according to the Schedule of Activities. Cetuximab infusions should be performed, if possible, on the same day of each week with no more than 3 days deviation.

The dose and administration procedure for cetuximab (first infusion and subsequent infusions) is described in Table 6.

Table 6 Dose and Administration Procedure for Cetuximab

	Dosage	Infusion rate	Flush of line with saline solution (0.9%) at the end of infusion	Prophylactic pretreatment with an appropriate antihistamine and corticosteroid
Infusions on Day 1 of each cycle during the chemotherapy cycles	250 mg/m^2	maximum 5 mg/minute	Yes	Recommended
Infusions on Day 8 of each cycle during the chemotherapy cycles	500 mg/m^2	maximum 10 mg/minute	Yes	Recommended
Subsequent infusions during the maintenance phase	500 mg/m^2	maximum 10 mg/minute	Yes	Recommended

Details on cetuximab dose modifications due to AEs are in Section 6.9.2.

The cetuximab dose will be based on the participant's body surface area (BSA). Recalculation of the BSA has to be repeated if the participant's body weight changes by more than 10% as compared to the last BSA calculation.

The BSA should be calculated according to the Mosteller formula: BSA (m^2) = sqrt ([height (cm) × weight (kg)] / 3600). The calculation will be based on the weight measured at each relevant visit and the height as measured and recorded at the screening visit.

The maximum infusion rate must NOT exceed 5 mg/minute for first infusion and must NOT exceed 10 mg/minute at subsequent infusions.

Pretreatment with an appropriate antihistamine and corticosteroids is mandatory approximately 1 hour before the first 2 cetuximab infusions. Premedication is recommended before all subsequent infusions of cetuximab.

Before, during, and up to 1 hour after each cetuximab infusion, participants must have their vital signs closely monitored to detect any AEs (specifically, allergic/hypersensitivity reactions). A physician should be available during each cetuximab administration, ie, until the complete infusion has been given and for 1 hour after the end of the infusion. Exact documentation of actual dose, date, start time, and end time of each cetuximab infusion is mandatory.

Cetuximab must not be mixed with any other substance and therefore requires a separate infusion line. If another iv infusion is required at the same time as the cetuximab infusion (example, for hydration), a second line must be used.

6.6.4 Chemotherapy

6.6.4.1 Gemcitabine and Cisplatin

Using the 3-week schedule, gemcitabine is administered iv at a dose of 1250 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle. Dose adjustments for hematologic toxicity may be required. If marrow suppression is noted, dose modifications are noted in Table 9. For non-hematologic toxicities, other than alopecia and nausea, dose modifications should be considered.

Cisplatin is administered intravenously at a dose of 75 mg/m^2 over 30 minutes or according to local standards on Day 1 of each 3-week cycle. Predosing should follow considerations in Table 7 or local standards. Participants who are receiving cisplatin must be monitored for nephrotoxicity, ototoxicity, and neuropathy in addition to myelosuppression. Dose adjustments for hematologic toxicity may be required. For non-hematologic toxicities, other than alopecia and nausea, dose modifications should be considered.

After the starting dose, dose modifications (dose delays and dose changes) for chemotherapy-related toxicity should be made in accordance with labeling instructions and local institutional guidelines. Discontinuation of chemotherapy due to AEs should also be in accordance with the chemotherapy label and local institutional practice (see Table 9).

Table 7 Predosing Considerations for Cisplatin

Issue/Indication	Recommended Steps
Pre-emesis	Follow current MASCC/ESMO[a] or NCCN[b] guidelines for chemotherapy-induced nausea and vomiting for a "high risk" regimen
Hydration/ nephrotoxicity	Per package insert/SmPC for cisplatin[c]. Cisplatin causes severe cumulative nephrotoxicity. A urine output of 100 mL/hour or greater will tend to minimize cisplatin nephrotoxicity. Adequate hydration must therefore be maintained to cause sufficient diuresis prior to, during and after treatment with cisplatin. Next to iv infusion, forced diuresis may be required and moreover participants are to be requested to drink appropriate quantities of liquids for 24 hours after cisplatin infusion to ensure adequate urine secretion.

Myelosuppression/ neutropenia	Refer to the current package insert/SmPC and local guidance for modifications in dose and schedule of cisplatin[c]. Cisplatin dose should be withheld if platelet count is less than 100,000 cells/mm^3 or neutrophil count is less than 1500 cells/mm^3. Primary prophylaxis with G-CSF in order to reduce the risk of febrile neutropenia (FN) is not recommended, according to ASCO[d] and ESMO guidelines. FN is defined as oral temperature > 38.5°C or 2 consecutive readings of > 38°C for 2 hours and an absolute neutrophil count < 0.5 × 10^9/L, or expected to fall below 0.5 × 10^9/L. Secondary prophylaxis with CSFs is recommended for participants who experienced a neutropenic complication from a previous cycle of chemotherapy (for which primary prophylaxis was not received), in which a reduced dose or treatment delay may compromise disease-free or OS or treatment outcome. The secondary prophylaxis should follow ASCO or ESMO or local guidelines. The dosage instructions should follow the local guidelines or the ASCO or ESMO guidelines.
Ototoxicity/ neurotoxicity	Per SmPC for cisplatin[c]. Cisplatin is proven to be cumulative ototoxic and neurotoxic. Neurologic examination and monitoring of potential ototoxicity is to be performed prior to each cisplatin dosing and during the treatment.

ASCO = American Society of Clinical Oncology, CSF = colony stimulating factor, ESMO = European Society for Medical Oncology, FN = febrile neutropenia, G-CSF = granulocyte-colony stimulating factor, iv = intravenous, MASCC = Multinational Association of Supportive Care in Cancer, NCCN = National Comprehensive Cancer Network, SmPC = summary of product characteristics, OS = overall survival.

[a] Annals of Oncology 21 (Supplement 5): v232–v243, 2010.

[b] NCCN Guidelines Antiemesis version 2/2016.

[c] https://www.medicines.org.uk/emc/medicine/25944.

[d] J Clin Oncol 33:3199-3212.

6.6.4.2 Carboplatin

For participants who discontinue treatment with cisplatin due to unacceptable toxicities, continuation of platinum-based treatment (up to 4 cycles in total) with carboplatin is allowed at the discretion of the Investigator. For these subjects, carboplatin is administered intravenously at AUC 5 using the Calvert formula, over 30 to 60 minutes on Day 1 of each 3-week cycle. Participants receiving carboplatin should be monitored for myelosuppression with thrombopenia, leucopenia, neutropenia and anemia; infections; hepatic toxicity; renal toxicity; nausea and vomiting; ototoxicity; and peripheral neuropathies (see Table 8).

Table 8 Predosing Consideration for Carboplatin

Adverse Reaction	Recommended Steps
Nausea or vomiting	Follow current MASCC/ESMO or NCCN[a] guidelines for chemotherapy-induced nausea and vomiting for a "high risk" regimen
Hematological toxicities	Per package insert/SmPC of carboplatin[b] can cause leukopenia, neutropenia, and thrombocytopenia which are dose-dependent and dose-limiting. Peripheral blood counts should be monitored before start of treatment with carboplatin and then at weekly intervals and, in case of toxicity, until recovery is achieved.
Neurotoxicity	Refer to the current package insert/SmPC and local guidance for modifications in dose and schedule. Carboplatin dose should be reduced for Grade 3 or Grade 4 neurotoxicity.
Renal toxicity	Per SmPC of carboplatin, impairment of renal function is more likely in patients who have previously experienced nephrotoxicity as a result of cisplatin therapy.

	Dosage reduction or discontinuation of carboplatin therapy is required in the presence of severe alteration in renal function tests.
Ototoxicity	Auditory defects have been reported during carboplatin therapy; concomitant use of Carboplatin with aminoglycosides should be approached with caution because of nephrotoxicity and ototoxicity, particularly in patients with kidney failure.

ESMO = European Society for Medical Oncology, MASCC = Multinational Association of Supportive Care in Cancer, NCCN = National Comprehensive Cancer Network, SmPC = summary of product characteristics.

[a]NCCN Guidelines Antiemesis version 2/2016.

[b] https://www.medicines.org.uk/emc/product/3787/smpc

*Carboplatin should be discontinued in case of severe and persistent myelosuppression as per SmPC recommendation.

Table 9 Dose Modification for Chemotherapy

Dose Level	Gemcitabine	Cisplatin	Carboplatin
Starting dose	1250 mg/m^2	75 mg/m^2	AUC 5*
First dose reduction	950 mg/m^2	56 mg/m^2	AUC 3.75*
Second dose reduction	625 mg/m^2	38 mg/m^2	AUC 2.5*
Third dose reduction	Discontinue	Discontinue	Discontinue
*using the Calvert formula			

6.6.5 Treatment Beyond Disease Progression and Complete Response

6.6.5.1 Treatment Beyond Progression

6.6.5.1.1 Treatment Beyond Initial Progression

Participants will receive avelumab and cetuximab as outlined in the Schedule of Activities until disease progression.

Avelumab and cetuximab may continue past the initial determination of disease progression according to RECIST v1.1 as long as the following criteria are met:

- Cetuximab may only be continued if treatment with avelumab is also ongoing.
- No new unacceptable treatment or disease-related toxicity.
- Tolerance of study interventions.
- Stable ECOG PS.
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (for example, central nervous system metastases).

A radiographic assessment should be performed after 4 weeks but no later than 6 weeks of original PD to determine whether there has been a decrease in the tumor size, or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the participant is clinically deteriorating and unlikely to receive any benefit from continued treatment with avelumab or avelumab and cetuximab.

6.6.5.1.2 Treatment beyond confirmed progression

After confirmed PD, if the Investigator feels that the participant continues to achieve clinical benefit by continuing treatment, the participant should remain on the study and continue to receive monitoring according to the Schedule of Activities. The decision to continue treatment beyond confirmed PD should be discussed with the Medical Monitor and documented in the study records. Participants who continue beyond progression will be evaluated for further tumor response as per the protocol schedule. Treatment should be discontinued permanently upon documentation of further, unequivocal disease progression unless there are no alternative therapeutic options and the benefit/risk assessment is favorable in consultation between the Investigator and the Medical Monitor. In case of continuation of treatment beyond PD, treatment will be discontinued once any other criteria for withdrawal are met (See Section 7.1).

6.6.5.2 Continuation of study intervention after local treatment of disease progression:

If disease progression is due to brain metastasis, participants may continue study interventions after the local treatment of the brain lesions provided that the above criteria are met in addition to the following:

- Tumor assessment showing disease progression has been performed and was documented according to RECIST v1.1 prior to the procedure.
- Brain metastases have been treated locally and are clinically stable for at least 2 weeks prior to re-initiation of study interventions.
- There are no ongoing neurological symptoms that are related to the brain localization of the disease (sequelae that are a consequence of the treatment of the brain metastases are acceptable).
- Participants must be either off steroids or on a stable or decreasing dose of $\leq$ 10 mg daily prednisone (or equivalent).
- Benefit/risk assessment to continue study intervention is favorable under consideration of any alternative treatment options as assessed by the Investigator.

In addition, if disease progression is mainly due to a metastatic lesion which in the opinion of the Investigator may be surgically removed, participants may continue study interventions after the local treatment of such a lesion provided that:

- Tumor assessment showing disease progression has been performed and was documented according to RECIST v1.1 prior to the procedure.
- It has been at least 2 weeks and the participant has fully recovered from the surgery.
- Benefit/risk assessment to continue study intervention is favorable under consideration of any alternative treatment options as assessed by the Investigator.

6.6.5.3 Treatment Beyond Complete Response

Additionally, participants receiving avelumab who have experienced a CR should be treated for a minimum of 12 months based on clinical judgment of benefit and/or until disease progression or unacceptable toxicity, after confirmation of response at the discretion of the Investigator. In case such participant's disease relapses after stopping treatment, but prior to the end of the study, 1 re-initiation of treatment is allowed at the discretion of the Investigator and agreement with the Medical Monitor. To be eligible for re-treatment, the participant must not have experienced any toxicity that leads to treatment discontinuation of the initial avelumab. Participants who re-initiate treatment will stay on study and will be treated and monitored according to the protocol and the "until progression" schedule in the Schedule of Activities.

6.7 Study Intervention after the End of the Study

After a participant has completed the study or has withdrawn early, usual treatment will be administered, if required, in accordance with the study site's standard of care and generally accepted medical practice and depending on the participant's individual medical needs. The Sponsor will not provide any additional care to participants after they leave the study because such care should not differ from what is normally expected for patients with NSCLC.

Participants will be followed for survival, subsequent use of anti-cancer therapy and AEs as specified in the Schedule of Activities. Follow-up may be performed by phone.

Survival follow-up will continue until up to 12 months after the last participant receives the last dose of avelumab/cetuximab. Sponsor may terminate the study at any time and there may be allowance for participants to enter a roll over study, expanded access, or other mechanism for avelumab and cetuximab access as appropriate.

6.8 Special Precautions

6.8.1 Avelumab

As a routine precaution, participants enrolled in this study must be observed for 2 hours post avelumab infusion for the first 4 avelumab infusions, and then according to clinical signs and symptoms, in an area with resuscitation equipment and emergency agents. At all times during avelumab treatment, immediate emergency treatment of an infusion-related reaction or a severe hypersensitivity reaction according to institutional standards must be assured. In order to treat possible hypersensitivity reactions, for instance, dexamethasone 10 mg and epinephrine in a 1:1000 dilution or equivalents should always be available along with equipment for assisted ventilation.

The treatment recommendations for infusion-related reactions are outlined in Table 10.

Investigators should also monitor participants closely for potential irAEs, which may become manifest at any time during treatment. Such events include but are not limited to pneumonitis, hepatitis, colitis, endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type

1 diabetes mellitus), myocarditis, myositis, and rash. See Section 6.9.1 for details on the management of irAEs.

Immediate access to an Intensive Care Unit or equivalent environment and appropriate medical therapy (including epinephrine, corticosteroids, iv antihistamines, bronchodilators, and oxygen) must be available for use in the treatment of infusion-related reactions. Infusion of avelumab will be stopped in case of Grade ≥ 2 infusion-related, allergic, or anaphylactoid reactions.

If hypersensitivity reaction occurs, the participant must be treated according to the best available medical practice. Participants should be instructed to report any delayed reactions to the Investigator immediately.

On days where several study interventions are scheduled, administration of premedication including a corticosteroid, an antihistamine, and paracetamol prior to the cetuximab infusion, which is always administered before avelumab, is acceptable. However, if the avelumab infusion is given more than 4 hours after the initial premedication, a new sequence of premedication has to be administered before the avelumab infusion.

6.8.2 Cetuximab

Participants should be monitored for at least 1 hour following cetuximab infusions in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis (for example, epinephrine, corticosteroids, iv antihistamines, bronchodilators, and oxygen). Monitoring should be longer to confirm resolution of the event in patients requiring treatment for infusion reactions.

6.8.3 Gemcitabine, Cisplatin, and Carboplatin

Gemcitabine

Gemcitabine dosage adjustment for hematologic toxicities is based upon the granulocyte and platelet counts on the day of treatment. Participants receiving gemcitabine should be monitored prior to each dose using complete blood counts.

Cisplatin

Participants who receive cisplatin must be monitored for nephrotoxicity, ototoxicity, and neuropathy in addition to myelosuppression. Cisplatin should not be employed in participants with hearing impairment. Caution must be observed in the case of nausea, vomiting, and dehydration. Premedication with anti-emetics and hydration are performed according to local standards and the SmPC.

Carboplatin

Participants who switch to treatment with carboplatin after experiencing cisplatin-related toxicities should be monitored for symptoms of myelosuppression with thrombopenia, leucopenia, neutropenia and anemia; infections; nausea and vomiting; hepatic toxicity, renal toxicity, ototoxicity; and peripheral neuropathies as per SmPC recommendations. Premedication with anti-emetics should be performed according to local treatment standards.

6.9 Management of Adverse Events of Interest

6.9.1 Avelumab

Infusion-related reactions and irAEs should be handled according to the following guidelines.

Infusion-Related Reactions

In order to mitigate infusion-related reactions, participants have to be premedicated with an antihistamine and with paracetamol (acetaminophen) prior to the first 4 infusions of avelumab. Premedication should be administered for subsequent avelumab doses based upon clinical judgment and presence/severity of prior infusion reactions.

Management of infusion-related reactions should follow guidelines set forth in Table 10.

Table 10 Treatment Modification for Symptoms of Infusion-related Reactions Associated with Avelumab

NCI-CTCAE Grade	Treatment Modification for Avelumab
Grade 1 – mild • Mild transient reaction; infusion interruption not indicated; intervention not indicated.	• Decrease the avelumab infusion rate by 50% and monitor closely for any worsening.
Grade 2 – moderate • Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, iv fluids); prophylactic medications indicated for ≤ 24 hours.	• Temporarily discontinue avelumab infusion. • Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any worsening.
Grade 3 or Grade 4 – severe or life-threatening • Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. • Grade 4: Life-threatening consequences; urgent intervention indicated.	• Stop the avelumab infusion immediately and disconnect infusion tubing from the participant. • Participants have to be withdrawn immediately from avelumab treatment and must not receive any further avelumab treatment.

iv = intravenous, NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Event, NSAIDs = nonsteroidal anti-inflammatory drugs.

Immune-Related Adverse Events

Since inhibition of PD-L1 stimulates the immune system, irAEs may occur. Treatment of irAEs is mainly dependent upon severity (NCI-CTCAE Grade):

- Grade 1 to 2: treat symptomatically or with moderate dose steroids, more frequent monitoring.
- Grade 1 to 2 (persistent): manage similar to high grade AE (Grade 3 to 4).
- Grade 3 to 4: treat with high dose corticosteroids.

Treatment of irAEs should follow guidelines set forth in Table 11.

Table 11 Management of Immune-Related Adverse Events

Gastrointestinal irAEs		
Severity of Diarrhea/Colitis (NCI-CTCAE v5.0)	**Initial Management**	**Follow-up Management**
Grade 1 Diarrhea: < 4 stools/day over Baseline Colitis: asymptomatic	Continue avelumab therapy Symptomatic treatment (eg, loperamide)	Close monitoring for worsening symptoms Educate participant to report worsening immediately If worsens: Treat as Grade 2, 3 or 4.
Grade 2 Diarrhea: 4 to 6 stools per day over Baseline; iv fluids indicated < 24 hours; not interfering with ADL Colitis: abdominal pain; blood in stool	Withhold avelumab therapy Symptomatic treatment	If improves to Grade ≤ 1: Resume avelumab therapy If persists > 5-7 days or recurs: Treat as Grade 3 or 4.
Grade 3 to 4 Diarrhea (Grade 3): ≥ 7 stools per day over Baseline; incontinence; iv fluids ≥ 24 hours; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation	Withhold avelumab for Grade 3. Permanently discontinue avelumab for Grade 4 or recurrent Grade 3. 1.0 to 2.0 mg/kg/day prednisone iv or equivalent Add prophylactic antibiotics for opportunistic infections Consider lower endoscopy	If improves: Continue steroids until Grade ≤ 1, then taper over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3). If worsens, persists > 3 to 5 days, or recurs after improvement: Add infliximab 5 mg/kg (if no contraindication). Note: infliximab should not be used in cases of perforation or sepsis.
Dermatological irAEs		
Grade of Rash (NCI-CTCAE v5.0)	**Initial Management**	**Follow-up Management**
Grade 1 to 2 Covering ≤ 30% body surface area	Continue avelumab therapy Symptomatic therapy (for example, antihistamines, topical steroids)	If persists > 1 to 2 weeks or recurs: Withhold avelumab therapy Consider skin biopsy Consider 0.5-1.0 mg/kg/day prednisone or equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy following steroids taper. If worsens: Treat as Grade 3 to 4.

Grade 3 to 4 Grade 3: Covering > 30% body surface area; Grade 4: Life-threatening consequences	Withhold avelumab for Grade 3. Permanently discontinue for Grade 4 or recurrent Grade 3. Consider skin biopsy Dermatology consult 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections	If improves to Grade ≤ 1: Taper steroids over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3).
Pulmonary irAEs		
Grade of Pneumonitis (NCI-CTCAE v5.0)	**Initial Management**	**Follow-up Management**
Grade 1 Radiographic changes only	Consider withholding avelumab therapy Monitor for symptoms every 2 to 3 days Consider Pulmonary and Infectious Disease consults	Re-assess at least every 3 weeks If worsens: Treat as Grade 2 or Grade 3 to 4.
Grade 2 Mild to moderate new symptoms	Withhold avelumab therapy Pulmonary and Infectious Disease consults Monitor symptoms daily; consider hospitalization 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	Re-assess every 1 to 3 days If improves: When symptoms return to Grade ≤ 1, taper steroids over at least 1 month, and then resume avelumab therapy following steroids taper If not improving after 2 weeks or worsening or for recurrent Grade 2: Treat as Grade 3 to 4.
Grade 3 to 4 Grade 3: Severe new symptoms; New/worsening hypoxia; Grade 4: Life-threatening	Permanently discontinue avelumab therapy. Hospitalize. Pulmonary and Infectious Disease consults. 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	If improves to Grade ≤ 1: Taper steroids over at least 1 month If not improving after 48 hours or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, iv immunoglobulin, or mycophenolate mofetil)
Hepatic irAEs		
Grade of Liver Test Elevation (NCI-CTCAE v5.0)	**Initial Management**	**Follow-up Management**
Grade 1	Continue avelumab therapy	Continue liver function monitoring If worsens: Treat as Grade 2 or 3 to 4.

Grade 1 AST or ALT > ULN to 3.0 x ULN and/or Total bilirubin > ULN to 1.5 x ULN		
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and/or total bilirubin > 1.5 to ≤ 3 x ULN	Withhold avelumab therapy Increase frequency of monitoring to every 3 days.	If returns to Grade ≤ 1: Resume routine monitoring; resume avelumab therapy. If elevation persists > 5 to 7 days or worsens: Treat as Grade 3 to 4.
Grade 3 to 4 AST or ALT > 5 x ULN and/or total bilirubin > 3 x ULN	Permanently discontinue avelumab therapy Increase frequency of monitoring to every 1 to 2 days 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consult gastroenterologist/ hepatologist. Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted	If returns to Grade ≤ 1: Taper steroids over at least 1 month If does not improve in > 3 to 5 days, worsens or rebounds: Add mycophenolate mofetil 1 gram (g) twice daily If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines.
Renal irAEs		
Grade of Creatinine Increased (NCI-CTCAE v5.0)	**Initial Management**	**Follow-up Management**
Grade 1 Creatinine increased > ULN to 1.5 x ULN	Continue avelumab therapy	Continue renal function monitoring If worsens: Treat as Grade 2 to 3 or 4.
Grade 2 to 3 Creatinine increased > 1.5 and ≤ 6 x ULN	Withhold avelumab therapy Increase frequency of monitoring to every 3 days 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy	If returns to Grade ≤ 1: Taper steroids over at least 1 month, and resume avelumab therapy following steroids taper. If worsens: Treat as Grade 4.
Grade 4 Creatinine increased > 6 x ULN	Permanently discontinue avelumab therapy Monitor creatinine daily 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy Nephrology consult	If returns to Grade ≤ 1: Taper steroids over at least 1 month.

Cardiac irAEs		
Myocarditis	**Initial Management**	**Follow-up Management**
New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (eg, troponin, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis.	Withhold avelumab therapy. Hospitalize. In the presence of life-threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management. Cardiology consult to establish etiology and rule-out immune-mediated myocarditis. Guideline based supportive treatment as per cardiology consult.[a] Consider myocardial biopsy if recommended per cardiology consult.	If symptoms improve and immune-mediated etiology is ruled out, re-start avelumab therapy. If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis.
Immune-mediated myocarditis	Permanently discontinue avelumab. Guideline based supportive treatment as appropriate as per cardiology consult. [a] 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections.	Once improving, taper steroids over at least 1 month. If no improvement or worsening, consider additional immunosuppressants (eg, azathioprine, cyclosporine A).
[a] Local guidelines, or eg. ESC or American Heart Association (AHA) guidelines ESC guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines AHA guidelines website: http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001		

Endocrine irAEs		
Endocrine Disorder	**Initial Management**	**Follow-up Management**
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, Type I diabetes mellitus)	Continue avelumab therapy Endocrinology consult if needed Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (ie, hypopituitarism / hypophysitis)	Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.

Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Withhold avelumab therapy Consider hospitalization Endocrinology consult Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (ie, hypopituitarism / hypophysitis)	Resume avelumab once symptoms and/or laboratory tests improve to Grade ≤ 1 (with or without hormone replacement/suppression). Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Hypopituitarism/Hypophysitis (secondary endocrinopathies)	If secondary thyroid and/or adrenal insufficiency is confirmed (ie, subnormal serum FT4 with inappropriately low TSH and/or low serum cortisol with inappropriately low ACTH) : • Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women) • Hormone replacement/suppressive therapy as appropriate • Perform pituitary MRI and visual field examination as indicated **If hypophysitis confirmed:** • Continue avelumab if mild symptoms with normal MRI. Repeat the MRI in 1 month. • Withhold avelumab if moderate, severe or life-threatening symptoms of hypophysitis and/or abnormal MRI. Consider hospitalization. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month. • Add prophylactic antibiotics for opportunistic infections.	Resume avelumab once symptoms and hormone tests improve to Grade ≤ 1 (with or without hormone replacement). In addition, for hypophysitis with abnormal MRI, resume avelumab only once shrinkage of the pituitary gland on MRI/CT scan is documented. Continue hormone replacement/suppression therapy as appropriate.
Other irAEs (not described above)		
Grade of other irAEs (NCI-CTCAE v5.0)	**Initial Management**	**Follow-up Management**
Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE	Withhold avelumab therapy pending clinical investigation	If irAE is ruled out, manage as appropriate according to the diagnosis and consider re-starting avelumab therapy If irAE is confirmed, treat as Grade 2 or 3 irAE.

Grade 2 irAE or first occurrence of Grade 3 irAE	Withhold avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If improves to Grade ≤ 1: Taper steroids over at least 1 month and resume avelumab therapy following steroids taper.
Recurrence of same Grade 3 irAEs	Permanently discontinue avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If improves to Grade ≤ 1: Taper steroids over at least 1 month.
Grade 4	Permanently discontinue avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent and/or other immunosuppressant as needed Add prophylactic antibiotics for opportunistic infections Specialty consult.	If improves to Grade ≤ 1: Taper steroids over at least 1 month
Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than hormonal replacement for adrenal insufficiency Persistent Grade 2 or 3 irAE lasting 12 weeks or longer	Permanently discontinue avelumab therapy Specialty consult	

ACTH = Adrenocorticotropic hormone, ADL = activities of daily living, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BNP = Brain natriuretic peptide, CK-MB = creatine kinase-muscle/brain, CT = computed tomography, FT4 = Free Thyroxine, GH = growth hormone, IGF-1 = insulin-like growth factor-1, irAE = immune-related adverse event, iv = intravenous, LH = luteinizing hormone, MRI = magnetic resonance imaging, NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Event, PRL = plasma prolactin, T4 = free thyroxine, TSH =, ULN = upper limit of normal.

6.9.2 Cetuximab

Skin Reactions

Prophylactic use of oral tetracyclines is highly recommended for participants receiving cetuximab for reducing the incidence of Grade 3 skin reactions. Unless there are contraindications based on participant and/or health care provider factors, prophylactic systemic treatment with minocycline 100 mg daily or doxycycline 100 mg twice daily is recommended for 6-8 weeks, starting 1 day before the administration of the first dose of cetuximab. The recommended prophylaxis for skin toxicities are described in Table 12.

Table 12 Recommended Prophylaxis for Skin Toxicities

Treatment	Dose	Start	Stop	Alternatives
		Systemic therapy[a]		
Minocycline	1 × 100 mg/day	Day 1	6-8 weeks[b]	In case of intolerance:

Treatment	Dose	Start	Stop	Alternatives
Or Doxycycline	2 × 100 mg/day			• First generation cephalosporins • Amoxicillin • Erythromycin • Limecycline
	Topical therapy			
Low potency steroid creams such as: • Alclometasone 0.05% • Desonide 0.05% • Fluocinolone 0.01%	2 × daily on face and chest	Day -1	6-8 weeks	
Emollient (creams or ointments)	3 × daily to the hands, and after hand washing 2 × daily on the rest of the body	Day -1	Continue	

[a] If infection is suspected (yellow crusts, purulent discharge, painful skin / nares), obtain culture and change to oral antibiotic based on sensitivities.

[b] May be continued beyond 6-8 weeks at the Investigator's discretion in the event of CTCAE Grade 2 rash.

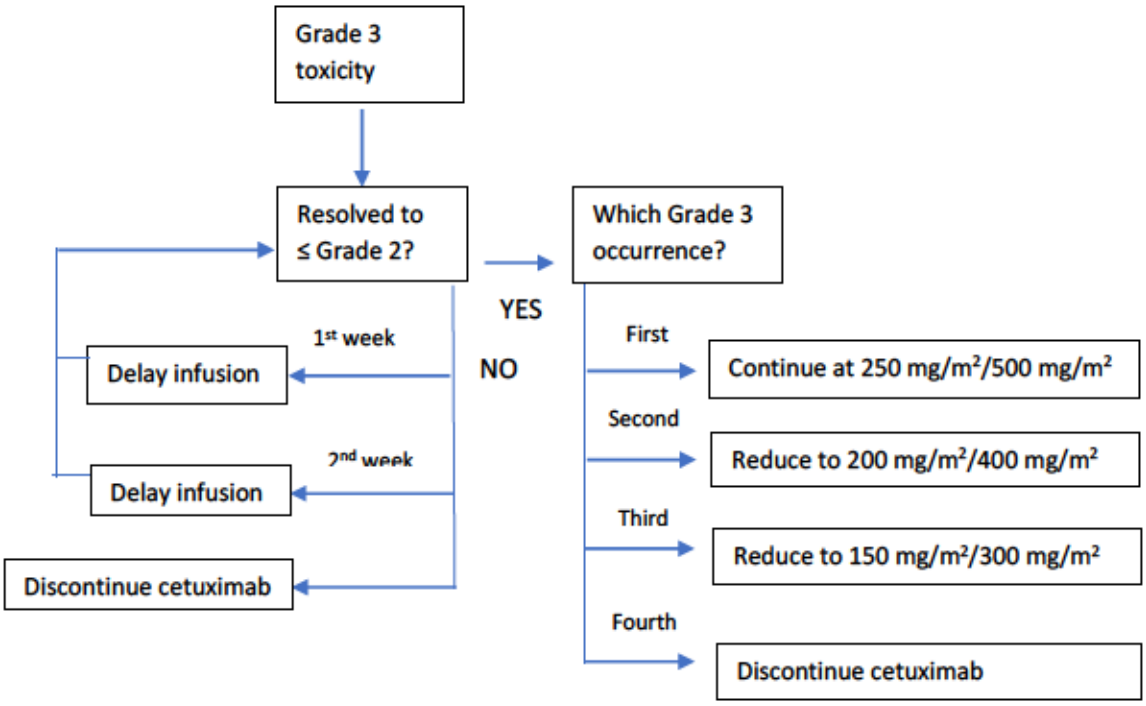
For a Grade 1 or 2 acne-like rash (as defined in the CTCAE v 5), treatment with topical antibiotics (for example, benzoylperoxide, erythromycin) or systemic antibiotics (for example, oral tetracyclines) should be considered. Participants with at least Grade 3 reactions should be referred to a dermatologist for advice and management if needed. If pruritus occurs, an oral antihistamine is advised. In the case of dry skin, the use of emollient creams is beneficial. Fissures may occur in dry skin and topical dressings are helpful.

If a participant experiences a Grade 3 skin reaction (as defined in the CTCAE v5), cetuximab treatment may be delayed for up to 14 days (omission of 1 or 2 scheduled administrations) without changing the dose level. If skin reactions resolve to Grade 2 or less by the following treatment period, treatment may be resumed.

If Grade 3 skin reactions occur for a second and third time, cetuximab treatment may again be delayed for up to 14 days with dose reductions to 200 mg/m² and then 150 mg/m² (based on 250 mg/m² initial dose), or dose reductions to 400 mg/m² and then 300 mg/m² (based on 500 mg/m² initial dose, see Figure 2). Cetuximab dose reductions are permanent. Participants must discontinue cetuximab if more than 2 consecutive infusions are withheld or Grade 3 skin reactions occur for a fourth time despite the appropriate dose reduction. Any Grade 4 toxicity (including skin reactions) considered related to cetuximab is to result in discontinuation of cetuximab treatment permanently.

If, in the opinion of the Investigator, the discontinuation of cetuximab is considered necessary, the participant should be withdrawn from cetuximab treatment immediately, but can be further treated with avelumab and remain on the study for scheduled visits if the individual toxicity is determined to be solely attributed to cetuximab per the Investigator.

Figure 2 **Treatment Adjustment in the Event of Grade 3 Skin Reactions Considered to be Related to Cetuximab (250 mg/m^2 Dose and 500 mg/m^2 Dose)**



Infusion-related Reactions

Mild or moderate infusion-related reactions are very common. Symptoms include fever, chills, dizziness or dyspnea occurring in a close temporal relationship mainly to the first cetuximab infusion.

Severe infusion-related reactions may occur, in some cases with a fatal outcome. Some of these reactions may be anaphylactoid/anaphylactic in nature or represent a cytokine release syndrome. This syndrome typically occurs within 1 hour after infusion and is less commonly associated with bronchospasm and urticaria but may also occur for up to several hours after infusion or with subsequent infusions. Cytokine release syndrome is normally most severe in relation to the first infusion.

Symptoms of severe infusion-related reaction may include bronchospasm, urticaria, hypertension or hypotension, loss of consciousness, or shock. In rare cases angina pectoris, myocardial infarction, or cardiac arrest have been observed.

Anaphylactic reactions may occur as early as within a few minutes of the first infusion, for example, due to preformed immunoglobulin E antibodies cross-reacting with cetuximab. These reactions are commonly associated with bronchospasm and urticaria. They can occur despite the use of premedication.

These symptoms usually occur during the first infusion and up to 1 hour after the end of infusion but may happen several hours after or with subsequent infusions. It is recommended to warn participants of the possibility of such a late onset and to instruct them to contact their physician if symptoms of an infusion-related reaction occur. Special attention is recommended for participants with reduced performance status and pre-existing cardiopulmonary disease.

The Investigator must treat all symptoms of infusion-related reactions with the best available medical measures. Based on previous experience with cetuximab infusion-related reactions, the treatment guidelines given in Table 13, graded according to the NCI-CTCAE Version 5.0 should be followed:

Table 13 Treatment Adjustment for Symptoms of Cetuximab Infusion-related Reactions

CTCAE Grade [a]	Treatment adjustment for cetuximab
Grade 1 mild Transient flushing or rash; drug fever < 38°C;	Decrease the cetuximab infusion rate by 50% and monitor closely for any worsening. The total infusion time for cetuximab should not exceed 240 minutes.
Grade 2 moderate Rash: flushing; urticaria; dyspnea; drug fever ≥ 38°C	Stop cetuximab infusion and immediately administer treatment for symptoms. Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity and monitor closely for any worsening.
Grade 3 or Grade 4 severe or life-threatening Grade 3: Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension Grade 4 Anaphylaxis;	Stop the cetuximab infusion immediately and disconnect infusion tubing from the participant. Treat symptoms vigorously. Participants have to be withdrawn immediately from treatment and must not receive any further cetuximab treatment.

[a] Graded according to NCI-CTCAE, version 5.0.
CTCAE = Common Terminology Criteria for Adverse Events, NCI = National Cancer Institute.

Resumption of Cetuximab Treatment Following Infusion-related Reactions

Once the cetuximab infusion rate has been decreased after an infusion-related reaction, it must remain decreased for all subsequent infusions. If the participant has a second infusion-related reaction on the slower infusion rate of cetuximab, the infusion should be stopped and the participant should be withdrawn from cetuximab treatment permanently. If a participant experiences a Grade 3 or 4 infusion-related reaction (excluding fever) at any time, she/he must discontinue cetuximab immediately, but can be further treated with avelumab and chemotherapy and remain in the study for scheduled visits if the infusion reaction can be attributed to cetuximab only in the opinion of the Investigator.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

Participants must be withdrawn from study treatment if any of the following occurs:

- Participants meeting the definition of confirmed PD while on treatment based on RECIST v1.1. Participants who experience disease progression may continue treatment under conditions described in Section 6.6.5
    - In case of premature withdrawal from the study treatment for reasons other than PD, the participants will be asked to attend scheduled visits including tumor assessment and other assessments as planned until confirmed PD and end of study or death.
- Significant clinical deterioration (clinical progression), defined as new symptoms that are deemed by the Investigator to be clinically significant or significant worsening of existing symptoms.
- Unacceptable toxicity.
- Withdrawal of consent from further treatment: In case of selective withdrawal from study treatment other study-related procedures and assessments should be continued as planned.
- Withdrawal of consent from further study participation: Participants should be explicitly asked at the time of withdrawal of consent if they would allow collected samples to be used and survival information to be collected, including verification of medical/public records as permitted by local regulations. These responses should accordingly be captured in the eCRF.
- Occurrence of an exclusion criterion, which is clinically relevant and affects the participant's safety, if study treatment discontinuation is considered necessary by the Investigator and/or Sponsor.
- Therapeutic failure requiring urgent additional or alternative anti-cancer treatment.
- Occurrence of AEs resulting in the permanent discontinuation of the trial treatment being desired or considered necessary by the Investigator and/or the participant.
- Occurrence of pregnancy in a female study participant.
- Use of a prohibited concomitant medication, as defined in Section 6.5 where the predefined consequence is withdrawal from the study treatment if considered necessary by the Investigator or the Sponsor.
- Noncompliance if the benefit/risk for continuation of treatment is negative according to Investigator's assessment.

The SoA specifies the data to collect at study intervention discontinuation and follow-up, and any additional evaluations that need to be completed (Section 1.3).

7.1.1 Rechallenge

Rechallenge with study intervention after discontinuation due to adverse events is allowed as defined in Section 6.9 (Management of Adverse Events of Interest).

If patients discontinue the study intervention for a confirmed complete response, 1 re-initiation of study intervention is permitted.

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time, at his/her own request (ie, withdrawal of consent), and without giving a reason.
- The participant may be withdrawn by the Investigator due to participation in another clinical study. However, participants will continue to be followed for documentation of further anti-cancer therapy and for survival.
- The participant may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.
- The Schedule of Activities (SoA) (Section 1.3) specifies the data to collect at study discontinuation and follow-up, and any additional evaluations that need to be completed. The appropriate End of Safety Follow-up electronic case report form (eCRF) page must be completed.

Withdrawal of consent will be considered withdrawal from the study unless the participant agrees to participate in further study-related assessments and/or agrees to be followed for survival. Participants should be explicitly asked at the time of withdrawal of consent if they would allow usage of their samples and further study-related assessments, especially tumor assessment, safety-related assessments, documentation of further anti-cancer therapy, or survival information to be collected including verification of medical/public records or contacting of the participant's primary physician or family as permitted by local regulations. These responses should accordingly be captured in the CRF.

If a participant fails to attend scheduled study assessments, the Investigator must determine the reasons and the circumstances as completely and accurately as possible.

If a participant is withdrawn prior to disease progression for any reason, the participant will not be replaced.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain if the participant wants to or should continue in the study.
- Before a participant is deemed "lost to follow-up", the Investigator or designee must make every effort to regain contact with the participant: 1) where possible, make 3 telephone calls; 2) if necessary, send a certified letter (or an equivalent local method) to the participant's last known mailing address, and 3) if a participant has given the appropriate consent and allowed according to local regulations, contact the participant's general practitioner or family for information. These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8 Study Assessments and Procedures

- Study assessments and procedures and their timing are summarized in the SoA.
- No protocol waivers or exemptions are allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened, to confirm eligibility, and if applicable, record reasons for screening failure.
- Prior to performing any study assessments that are not part of the participant's routine medical care, the Investigator will obtain written informed consent as specified in Appendix 2 (Study Governance).
- Procedures conducted as part of the participant's routine medical care (for example, blood count) and obtained before signing of the ICF may be used for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Sample collection, details of blood volume by visit and assessment, labeling, storage, and shipment requirements will be summarized in a separate Laboratory Manual or Manual of Operations.

8.1 Efficacy Assessments and Procedures

Computed tomography / magnetic resonance imaging (MRI) scans will be performed and collected until disease progression is assessed by the Investigators according to RECIST v1.1 or start of new anti-cancer therapy.

Radiographic images and physical findings (physical assessments) will be used by the Investigators for the local determination of disease progression and patient's treatment decisions.

For each participant, tumor response assessment will be performed by CT scan or MRI (if MRI is used, chest CT is mandatory) imaging of the chest/abdomen/pelvis (plus other regions as specifically required) and other established assessments of tumor burden if CT/MRI imaging is insufficient for the individual participant. All the scans performed at baseline and other imaging performed as clinically required (other supportive imaging) need to be repeated at subsequent visits. In general, lesions detected at baseline need to be followed using the same imaging methodology and preferably the same imaging equipment at subsequent tumor evaluation visits.

For each participant, the Investigator will designate 1 or more of the following measures of tumor status to follow for determining response: CT or MRI images of primary and/or metastatic tumor masses, physical examination findings, and the results of other assessments. All available images collected during the trial period will be considered. The most appropriate measures to evaluate the tumor status of a participant should be used. The measure(s) to be chosen for sequential evaluation during the trial must correspond to the measures used to document the progressive tumor status that qualifies the participant for enrollment. The tumor response assessment will be performed and listed according to the Schedules of Assessments.

Treatment decisions will be made by the Investigator based on the Investigator's assessment of disease status. Investigator's assessment of objective tumor response to treatment will be performed according to RECIST v1.1 (all measurements should be recorded in metric notation, as described in RECIST v1.1.)

At baseline, tumor lesions will be categorized in target and non-target lesions as described in RECIST v1.1.

Results for these evaluations will be recorded with as much specificity as possible so that pre- and post-treatment results will provide the best opportunity for evaluating tumor response.

Any CR or PR should be confirmed, preferably at the scheduled 9-week interval, but no sooner than 4 weeks after the initial documentation of CR or PR.

The Investigator may perform scans in addition to a scheduled trial scan for medical reasons or if the Investigator suspects PD. Participants who withdraw from the trial for clinical or symptomatic deterioration before objective documentation of PD will be requested to undergo appropriate imaging to confirm PD. Every effort should be made to confirm a clinical diagnosis of PD by imaging according to RECIST v1.1.

CCI [redacted]

CCI

[redacted]

8.1.1.1 Overall Tumor Assessment (irRECIST)

Overall tumor assessment per timepoint will be derived from tumor response assessments obtained for measured lesions, non-target lesions, and new lesions, as defined in Table 14.

Table 14 irRECIST Overall Tumor Assessment

TMTB			Non-Target Lesions	New Non-Measured Lesions [a]	Overall Tumor Assessment
Assessment based on TMTB of Measured Lesions	Target Lesions	New Measured Lesions [a]			
irCR	irCR	irCR	Absent at BL/irCR	No	irCR
	irCR	irCR	irNN	Yes, No	irPR
	irCR	irCR	Absent at BL/irCR, irNN	Yes	irPR
	irCR	irCR	irNE	Yes, No	irPR
	irCR	irCR	irPD	Yes, No	irPD
	irCR	irCR	Absent at BL/irCR irNN, irNE	Unequivocal Progression	irPD
	irCR	None	Absent at BL/irCR	No	irCR
	irCR	None	irNN	Yes, No	irPR
	irCR	None	irNE	Yes, No	irPR
	irCR	None	Absent at BL/irCR	Yes	irPR
	irCR	None	irPD	Yes/No	irPD
	irCR	None	Absent at BL/irCR, irNN, irNE	Unequivocal Progression	irPD
	None	irCR	irCR	No	irCR
	None	irCR	irNN	Yes, No	irPR
	None	irCR	irNE	Yes, No	irPR
	None	irCR	irPD	Yes, No	irPD
	None	irCR	None	No	irCR
	None	irCR	None	Yes	irPR
	None	irCR	Absent at BL/irCR, irNN, irNE	Unequivocal Progression	irPD
irPR	irPR	irPR	Absent at BL/irCR, irNN, irNE	Yes, No	irPR
	irPR	irPR	Absent at BL/irCR, irNN, irNE	Unequivocal Progression	irPD
	irPR	None	Absent at BL/irCR, irNN, irNE	Yes, No	irPR
	irPR	None	Absent at BL/irCR, irNN, irNE	Unequivocal Progression	irPD
	None	irPR	Absent at BL/irCR, irNN, irNE	Yes, No	irPR [a]
	None	irPR	Absent at BL/irCR, irNN, irNE	Unequivocal Progression	irPD
irSD	irSD	irSD	Absent at BL/irCR,, irNN, irNE	Yes, No	irSD
	irSD	irSD	Absent at BL/irCR, irNN, irNE	Unequivocal Progression	irPD
	irSD	None	Absent at BL/irCR, irNN, irNE	Yes, No	irSD

TMTB			Non-Target Lesions	New Non-Measured Lesions [a]	Overall Tumor Assessment
Assessment based on TMTB of Measured Lesions	Target Lesions	New Measured Lesions [a]			
	irSD	None	Absent at BL/irCR, irNN, irNE	Unequivocal Progression	irPD
	None	irSD	Absent at BL/irCR, irNN, irNE	Yes, No	irSD
	None	irSD	irCR, irNN, irNE	Unequivocal Progression	irPD
irPD	irPD	irPD	Absent at BL/irCR, irNN or irNE	Yes, No, Unequivocal Progression	irPD
	irPD	None	Absent at BL/irCR, irNN or irNE	Yes, No, Unequivocal Progression	irPD
	None	irPD	irCR, irNN, irNE, or None	Yes, No, Unequivocal Progression	irPD
irNE	irNE, irSD or None	irNE	Absent at BL/irCR, irNN, irNE	Unequivocal Progression	irPD
	irNE	irNE, irSD or None	Absent at BL/irCR, irNN, irNE	Unequivocal Progression	irPD
	irNE, irSD or None	irNE	Absent at BL/irCR, irNN, irNE	Yes, No	irNE
	irNE	irNE, irSD or None	Absent at BL/irCR, irNN, irNE	Yes, No	irNE
N/A	None	None	irCR	No	irCR
	None	None	irCR	Yes	irNN
	None	None	Absent at BL/irCR, irNN, irNE	Unequivocal Progression	irPD
	None	None	irNN	Yes, No	irNN
	None	None	irPD	Yes, No	irPD
	None	None	irNE	Yes, No	irNE
	None	None	None	No	irND
	None	None	None	Yes	irNN
Any	Any	Any	irPD	Yes, No	irPD

[a] When there is no disease at baseline, but there is **at least 1 new measurable** lesion at a post-baseline timepoint, the OTA is irPD at that timepoint, and any assessment is possible at subsequent timepoints – irCR, irPR, irSD, irPD, or irNE. In addition, when there is no disease at baseline, but there are 1 or more **new non-measurable** lesions at a post-baseline timepoint, the OTA is irNN at that timepoint, and the possible assessments at subsequent timepoints are irCR, irNN, irPD, or NE.

NOTE: Worsening of non-target and/or new non-measured lesions has to be massive to drive an overall irPD by itself.

irCR = immune-related complete response, irND = immune-related no disease, irNE = immune-related not evaluable, irNN = immune-related noncomplete response, irPD = immune-related progressive disease, irPR = immune-related partial response, irSD = immune-related stable disease, NE = Not evaluable.

Tumor measurements to determine response will be performed every 9 weeks (starting Day 64/Week 10) for the first 6 months (until Week 28), and every 12 weeks thereafter. Response to treatment will be evaluated by RECIST v1.1 (primary and secondary efficacy endpoints) and by irRECIST (other efficacy endpoints). See Section 1.3 (Schedule of Activities) for further details.

The tumor response assessment will be performed as listed according to the Schedule of Activities by CT or MRI. In general, lesions detected during Screening need to be followed using the same methodology and preferably the same equipment at subsequent tumor assessment visits.

Additional efficacy analyses on BOR, DOR and PFS according to irRECIST evaluated by an independent review committee might be conducted retrospectively.

8.2 Safety Assessments and Procedures

The safety profile of the study treatments will be assessed through the recording, reporting, and analyzing of Baseline Medical Conditions, AEs, physical examination findings, including vital signs, 12-lead ECG and laboratory tests.

Comprehensive assessment of any apparent toxicity experienced by the participant will be performed throughout the course of the study, from the time of the participant's signature of informed consent. Study site personnel will report any AE, whether observed by the Investigator or reported by the participant.

See Appendix 4 for information relating to AEs and AESIs (Adverse events of special interest).

8.2.1 Physical Examinations

A physical examination will be conducted at Screening and at subsequent visits as indicated in the Schedule of Activities (Section 1.3) and documented in the eCRF. Abnormal findings are to be reassessed at subsequent visits.

A complete physical examination (including, general appearance, dermatological, pulmonary, cardiovascular, gastrointestinal, genitourinary, lymphatic, neurologic and musculoskeletal systems, head/neck, extremities, eyes, ears, nose, throat, and cognitive status) will be performed and the results documented. All newly diagnosed or worsening conditions, signs, and symptoms observed from screening, whether related to study treatment or not, are to be reported as AEs.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2 Vital Signs

As noted in Section 6.8.1, participants must have their vital signs closely monitored before, during, and up to 2 hours after each avelumab infusion for the first 4 infusions in an area with resuscitation equipment and emergency agents, and then according to clinical signs and symptoms, to detect any AEs (specifically, allergic/hypersensitivity reactions).

As noted in Section 6.8.2, participants must have their vital signs closely monitored before, during, and up to 2 hours after each cetuximab infusion, to detect any AEs (specifically,

allergic/hypersensitivity reactions). A physician should be available during each cetuximab administration, ie, until the complete infusion has been given and for 1 hour after the end of the infusion.

In addition, the below applies to all participants:

- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (for example, television, cell phones).

8.2.3 Electrocardiograms

Single 12-lead ECG will be obtained as outlined in the SoA using an ECG machine that automatically calculates the heart rate and measures PR, QRS, and QT intervals, after the participant has been in a supine position breathing quietly for 5 minutes. The ECG will be repeated at any other scheduled or unscheduled visit only if it is clinically warranted in the opinion of the Investigator.

8.2.4 Clinical Safety Laboratory Assessments

Blood and urine samples will be collected for the clinical laboratory tests listed in Appendix 6, at the time points listed in the SoA. All samples should be clearly identified.

Additional tests may be performed at any time during the study, as determined necessary by the Investigator or required by local regulations.

The tests that will be performed by the local laboratory are screening pregnancy testing, hepatitis B virus, hepatitis C virus testing, urinalysis, and urine pregnancy testing.

Samples for complete blood count and core chemistry must be available and reviewed prior to dose administration. Results of all local laboratory testing will be transferred to the clinical database.

Local laboratory samples will be drawn and are required to be recorded in the eCRFs. Additional local laboratories may be used at the discretion of the Investigator as clinically needed for safety management of the participant. Relevant local laboratory results will be recorded according to the eCRF completion guidelines when used to make any changes in treatment.

For female participants of childbearing potential, a serum β human chorionic gonadotropin pregnancy test will be carried out during the Screening phase (from serum) and at the visits indicated in the Schedule of Activities (from urine) (Section 1.3). Follicle stimulating hormone might be evaluated at Screening for confirmation of menopausal status.

In case of liver function test elevations (AST, ALT, and/or total bilirubin) requiring additional laboratory draws, an unscheduled laboratory draw should be sent to the laboratory for analysis.

Blood samples will be drawn, processed, and stored in accordance with directions provided in the Study Manual and as per timing shown in the Schedule of Activities.

The report of the results must be retained as a part of the participant's medical record or source documents. Blood samples for full safety tests will be taken from nonfasted participants as detailed in the Schedule of Activities. Free thyroxine, thyroid stimulating hormone, and urinalysis will only be assessed at the prespecified time points. If confirmation of a participant's postmenopausal status is necessary, an FSH level testing will also be performed at Screening.

The Investigator must review each laboratory report, document their review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents.

8.3 Adverse Events and Serious Adverse Events

The definitions of an Adverse Event (AE) and a Serious Adverse Event (SAE) are in Appendix 4.

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

The AE reporting period for safety surveillance begins when the subject is initially included in the trial (date of first signature of informed consent) and continues through the 30-days (± 5 days) Safety Follow-up visit. After the Safety Follow-up visit all SAEs and treatment-related non-serious AEs need to be documented up until the Safety Follow-up Phone Call, which is defined as 90 days (± 5 days) after last administration of study intervention.

Any SAE assessed as related to study intervention must be recorded and reported, as indicated in Appendix 4, whenever it occurs, irrespective of the time elapsed since the last administration of study intervention.

The method of recording, evaluating, and assessing causality of AEs (including SAEs) and the procedures for completing and transmitting SAE reports are in Appendix 4.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

At each study visit, the participant will be queried on changes in his or her condition. During the reporting period, any unfavorable changes in the participant´s condition will be recorded as AEs, regardless if reported by participant or observed by the Investigator.

Complete, accurate and consistent data on all AEs experienced for the duration of the reporting period (defined above) will be reported on an ongoing basis in the appropriate section of the CRF. All SAEs must be additionally documented and reported using the appropriate Report Form as specified in Appendix 4.

8.3.3 Follow-up of Adverse Events and Serious Adverse Events

AEs are recorded and assessed continuously throughout the study, as specified in Section 8.3.1 (Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information) and are assessed for their outcome at the 30-day Safety Follow-up visit. After this

visit, SAEs and treatment-related non-serious AEs are recorded and assessed continuously until the 90-day Safety Follow-up Phone Call.

At 90 days (± 5 days) after the last dose of study intervention, the Investigator will contact participants by telephone to collect information on new or ongoing Serious Adverse Events (SAEs) and treatment-related non-serious AEs. Any SAE assessed by the Investigator as related to study treatment must be reported whenever it occurs, irrespective of the time elapsed since the last administration of study treatment. In addition, such participants may be invited to the site for further evaluation at the Investigator's discretion. Participants will also be asked about any new antitumor therapy.

All SAEs ongoing at the 90-day Safety Follow-up Phone Call must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the participant is documented as "lost to follow-up". Reasonable attempts to obtain this information must be made and documented. It is also the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed. Further information on follow-up procedures is given in Appendix 4 (Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reports).

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

The Sponsor will send appropriate safety notifications to Health Authorities in accordance with applicable laws and regulations.

The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (particularly deaths) involving study participants to the Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) that approved the study.

In accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP), the Sponsor/designee will inform the Investigator of findings that could adversely affect the safety of participants, impact the conduct of the study or alter the IEC's/IRB's approval/favorable opinion to continue the study. In line with respective regulations, the Sponsor/designee will inform the Investigator of AEs that are both serious and unexpected and considered to be related to the administered product ("suspected unexpected serious adverse reactions" or SUSARs). The Investigator should place copies of Safety Reports in the Investigator Site File. National regulations regarding Safety Report notifications to Investigators will be considered.

When specifically required by regulations and guidelines, the Sponsor/designee will provide appropriate Safety Reports directly to the concerned lead IEC/IRB and will maintain records of these notifications. When direct reporting is not clearly defined by national or site-specific regulations, the Investigator will be responsible for promptly notifying the concerned IEC/IRB of any Safety Reports provided by the Sponsor/designee and of filing copies of all related correspondence in the Investigator Site File.

For studies covered by the European Directive 2001/20/EC, the Sponsor's responsibilities regarding the reporting of SAEs/SUSARs/Safety Issues will be carried out in accordance with that Directive and with the related Detailed Guidance documents.

8.3.5 Pregnancy

Only pregnancies the Investigator considers to be related to the study intervention (for example, resulting from a drug interaction with a contraceptive method) are AEs. However, all pregnancies with an estimated conception date during the period defined in Section 8.3.1 (from first dose to the EoT Visit) must be recorded in the AE page/section of the CRF for both pregnancies in female participants and pregnancies in female partners of male participants. The Investigator must notify the Sponsor/designee in an expedited manner of any pregnancy using the Pregnancy Report Form, which must be transmitted by the same process specified for SAE reporting in Appendix 4, section on Reporting Serious Adverse Events and Adverse Events of Special Interest.

Investigators must actively follow-up, document and report on the outcome of all these pregnancies, even if the participants are withdrawn from the study.

The Investigator must notify the Sponsor/designee of these outcomes using the Pregnancy Report Form. If an abnormal outcome occurs, the SAE Report Form will be used if the participant sustains an event and the Parent-Child/Fetus Adverse Event Report Form if the child/fetus sustains an event. Any abnormal outcome (for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) must be reported in an expedited manner, as specified in Section 8.3.1, while normal outcomes must be reported within 45 days after delivery.

In the event of a pregnancy in a female participant occurring during the study, the participant must be discontinued from study intervention. The Sponsor/designee must be notified without delay and the participant must be followed as indicated above.

8.4 Treatment of Overdose

Avelumab:

An overdose of avelumab is defined as any dose $\geq$ 10% than the dose for that particular administration.

There are no known symptoms of avelumab overdose to date. The Investigator should use his or her clinical judgment when treating an overdose of the study intervention

Cetuximab:

An overdose of cetuximab is defined as any dose greater than the highest daily dose included in a clinical study protocol or planned for an individual participant enrolled in the study.

To date, there is limited experience with single cetuximab doses higher than 400 mg/m^2 BSA or weekly administrations of cetuximab doses higher than 250 mg/m^2 BSA. In clinical studies with cetuximab doses up to 700 mg/m^2 given every 2 weeks, the safety profile was consistent with the safety profile described in the cetuximab IB.

Gemcitabine and Cisplatin or Carboplatin:

In the case of overdose of chemotherapy, the Investigator should provide any possible medical care and treatment in accordance with local medical practice.

Even if it not associated with an AE or a SAE, any overdose is recorded in the CRF and reported to drug safety in an expedited manner. Overdoses are reported on a SAE Report Form, following the procedure in Appendix 4, section on Reporting Serious Adverse Events and Adverse Events of Special Interest.

8.5 Pharmacokinetics

- Whole blood samples of approximately 2 mL will be collected for measurement of serum concentrations of cetuximab, as specified in the SoA (Section 1.3). The actual date and time (24-hour clock time) of each sample will be recorded.
- The quantification of cetuximab in serum will be performed using a validated immunoassay method. Concentrations will be used to evaluate the PK of cetuximab.
- Whole blood samples of approximately 2 mL will be collected for measurement of serum concentrations of avelumab, as specified in the SoA (Section 1.3). The actual date and time (24-hour clock time) of each sample will be recorded.
- The quantification of avelumab in serum will be performed using a validated immunoassay method. Concentrations will be used to evaluate the PK of avelumab.

Blood samples for PK determinations should be collected according to the appropriate Schedules of Assessments. Every effort should be made to collect samples per the scheduled timepoint and within the specified windows. The objective is for samples to be collected within the windows specified, but any excursions outside these windows will only be counted as protocol deviations if the time of the sample collection is not recorded or if the samples are not collected.

Remaining samples collected for analysis of cetuximab or avelumab serum concentration may also be used to evaluate immunogenicity and safety or efficacy aspects related to concerns arising during or after the study. Details on processes for collection and shipment of these samples are in the Laboratory Manual. The Sponsor will store the samples in a secure storage space with adequate measures to protect confidentiality. Retention time and possible analyses of samples after the end of study are specified in the respective ICF.

CCI [redacted]

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8.10 Immunogenicity Assessments

Whole blood samples of approximately 2 mL will be collected for detection of antibodies against cetuximab in serum, as specified in the SoA. (Section 1.3). Samples will be collected prior to any study intervention administration on the same Study Day.

The detection of antibodies to cetuximab will be performed using a validated immunoassay method with tiered testing of screening, confirmatory and titration. Confirmed positive antibodies may be further characterized.

Whole blood samples of approximately 2 mL will be collected for detection of antibodies against avelumab in serum, as specified in the SoA (Section 1.3). Samples will be collected prior to any study intervention administration on the same Study Day.

The detection of antibodies to avelumab will be performed using a validated immunoassay method with tiered testing of screening, confirmatory and titration. Confirmed positive antibodies may be further characterized.

CCI [redacted]

Details on processes for collection and shipment of these samples are in the Laboratory Manual. The Sponsor will store the samples in a secure storage space with adequate measures to protect confidentiality. Retention time and possible analyses of samples after the end of study are specified in the respective ICF.

9 Statistical Considerations

9.1 Statistical Hypotheses

No formal statistical hypothesis will be tested, as the study is designed to be CCI [redacted]

CCI [redacted]

CCI [redacted]

9.3 Populations for Analyses

The analysis populations are specified below. The final decision to exclude participants from any analysis population will be made during a data review meeting prior to database lock. For purposes of analysis, the analysis populations are defined in Table 15.

Table 15 Analysis Populations

Population	Description
Enrolled	All participants who sign informed consent
Full Analysis Set (FAS)/Safety Analysis Set	The FAS/Safety Analysis Set will include all participants who receive at least 1 dose of study treatment.
Pharmacokinetic	PK Analysis Set The PK Analysis Set will consist of all participants who receive at least 1 dose of avelumab and/or cetuximab, have no clinically important protocol deviations or important events affecting PK, and provide at least 1 measurable post-dose concentration. Participants will be analyzed according to the actual treatment they received. All PK analyses will be based on this analysis set.
Immunogenicity	ADA Analysis Set The ADA Analysis Set will consist of all participants who receive at least 1 dose of avelumab and/or cetuximab and have at least 1 valid ADA result. All ADA analyses will be based on this analysis set.

9.4 Statistical Analyses

9.4.1 Efficacy Analyses

Table 16 Efficacy Endpoints and Statistical Analysis Methods

Endpoint	Statistical Analysis Methods
Primary	Confirmed BOR rate, defined as the proportion of participants having achieved confirmed CR or PR as Best Overall Response, according to RECIST v1.1 assessed by Investigator (from the first dose of study intervention until disease progression, death from any cause, or last tumor assessment). Analysis of confirmed BOR rate and the calculation of the respective 95% CI will be done on the FAS.
Secondary	PFS, defined as the time (in months) from first treatment day to the date of the first documentation of objective PD according to RECIST v1.1 assessed by Investigator, or death due to any cause, whichever occurs first. DOR, defined for participants with confirmed CR or PR, as the time from first documentation of confirmed response to the date of first documentation of PD according to RECIST v1.1 (assessed by Investigator) or death due to any cause. OS, defined as the time from first treatment day to the date of death due to any cause.

	For time-to-event analyses, the Kaplan-Meier estimates will be provided. The confidence interval for the median will be calculated according to Brookmeyer 1982. All analyses for secondary endpoints will be performed on the FAS unless otherwise specified.
CCI [redacted]	

There is no formal significance level for this study and all analyses are considered descriptive.

Subgroup analyses regarding EGFR H-score (< 200, ≥ 200), between PD-L1 low and high expression levels (< 50%, ≥ 50% < 80%, ≥ 80% TPS based on 73-10 assay), and further variables, will be performed.

9.4.1.1 BOR According to RECIST v1.1

Best overall response (BOR) will be assessed based on reported overall timepoint responses at different evaluation time points from the start date until documented disease progression, according to the following rules. Only tumor assessments performed before the start of any further anti-cancer therapies will be considered in the assessment of BOR. Clinical deterioration will not be considered as documented disease progression.

BOR Based on Confirmed Responses:

- CR = at least 2 determinations of CR at least 4 weeks apart and before progression.
- PR = at least 2 determinations of PR or better (PR followed by PR or PR followed by CR) at least 4 weeks apart and before progression (and not qualifying for a CR).
- SD (applicable only to patient with measurable disease at baseline) = at least 1 SD assessment (or better) ≥ 6 weeks after start date and before progression (and not qualifying for CR or PR).
- Non-CR/non-PD (applicable only to patients with non-measurable disease at baseline) = at least 1 non-CR/non-PD assessment (or better) ≥ 6 weeks after date of first study treatment and before progression (and not qualifying for CR or PR).
- PD = progression ≤ 12 weeks after start date (and not qualifying for CR, PR or SD).
- Not Evaluable (NE): all other cases.

More details will be provided in the IAP.

CCI [redacted]

CCI [redacted]

9.4.2 Safety Analyses

Table 17 Safety Endpoints and Statistical Analysis Methods

Endpoint	Statistical Analysis Methods
Secondary	Occurrence of TEAEs and treatment-related AEs, treatment-related Grade ≥ 3 AEs, and immune-related AEs according to NCI-CTCAE v5.0. (descriptive tabulation)
CCI [redacted]	[redacted]

All safety analyses will be performed on the Safety Analysis set.

Adverse Events

All AEs will be coded according to the MedDRA, version 21.0 or higher. The severity of AEs will be graded using NCI-CTCAE v5.0 toxicity grades. Adverse events related to study treatment will be defined as any AE considered related to any study treatment. In addition, missing classifications concerning study treatment relationships will be considered related to the study drug(s).

Adverse events observed from the first dose until 30 days after last study treatment administration (ie, TEAEs) will be summarized according to MedDRA system organ classes and preferred terms. The incidence and type of the following will be analyzed:

- TEAEs and SAEs
- TEAEs and SAEs related to study treatment
- TEAEs with NCI-CTCAE Grades ≥ 3

- TEAEs related to study treatment with NCI-CTCAE Grades ≥ 3
- AEs leading to withdrawal, dose modifications, or permanent study treatment discontinuation
- Deaths.

Participants who terminate treatment will be displayed in a by-participant listing and summarized by primary withdrawal reason.

All reported deaths after first dose of study treatment as well as reasons for death will be tabulated (for all participants enrolled). Deaths within 30 days from last dose administration and deaths beyond this period up to 90 days follow-up and reasons for them will also be tabulated.

Laboratory Variables

Laboratory results will be classified by grade according to NCI-CTCAE v5.0. The worst on-study grades after the first study treatment will be summarized.

Shifts in toxicity grades from first treatment to highest grade will be displayed. Results for variables that are not part of NCI-CTCAE will be presented as below, within, or above normal limits. Only participants with post-baseline laboratory values will be included in these analyses.

Physical Examination

Physical examination, including vital signs (body temperature, respiratory rate, heart rate, and blood pressure), and 12-lead ECG, recorded at baseline and after end of study treatment will be presented. Further details will be provided in the IAP.

9.4.3 Other Analyses

General Considerations

The following statistics will be used to summarize the trial data (for example, Baseline Characteristics) unless otherwise specified:

- Continuous variables: number of non-missing observations, mean, standard deviation, median, minimum, and maximum, 95% confidence intervals for the mean, as appropriate.
- Categorical variables: frequencies and percentages.

Estimation of Individual PK Parameters

- Pharmacokinetic parameters will be calculated by the PK/PD Data Processing Group of QPD, Merck, Darmstadt, Germany, or by a CRO selected by the Sponsor, using standard non-compartmental methods and the actual administered dose. PK parameters will be calculated using the actual elapsed time since dosing. When the actual sampling time is missing, calculations will be performed using the scheduled time. Otherwise, there will be no further imputation of missing data. The actual collection intervals will be used in the calculation of urine and fecal parameters.

- Non-compartmental computation of pharmacokinetic parameters will be performed using the computer program PPD (Certara, L.P., 1699 S Hanley Road, St Louis, MO 63144, USA).
- The statistical software PPD may be used to produce tables, listings and figures, and in the calculation of PK Parameters if appropriate.

PK concentrations of avelumab and cetuximab will be summarized descriptively and may be pooled with data from other studies to conduct population PK analysis. Such population PK analysis, if conducted, will be issued as a separate report.

Integrated analyses across studies, such as the population PK analysis will be presented separately from the main clinical study report (CSR).

ADA/Immunogenicity

Individual participants will be categorized across all valid ADA results as ever-positive versus never-positive. ADA ever-positive participants will be further categorized as pre-existing, including treatment-boosted, versus treatment-emergent. ADA treatment-emergent participants will be further subdivided into transient positive and persistent positive.

Additional characterization and potential association with other study outcomes will be specified in the IAP finalized before database lock.

9.4.4 Sequence of Analyses

Main analysis is planned at 5 months after last patient first visit. Although no interim analyses are planned, unplanned analyses may be performed.

A Safety Monitoring Committee (SMC), consisting of permanent members from the Sponsor and CRO, the Coordinating Investigator, and other optional members with expertise in the management of cancer subjects, will review the safety data on a regular basis throughout the trial. The SMC will decide by consensus and provide their recommendation on the continuation or suspension of enrollment after an initial safety run-in of cetuximab in combination with avelumab plus gemcitabine and cisplatin and will review all available safety data. The specific working procedures will be described in an SMC charter, which will be established prior to the start of recruitment.

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11 Appendices

Appendix 1 Abbreviations

ADA	Antidrug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BOR	Best overall response
BSA	Body surface area
CI	Confidence interval
C_{max}	Maximum observed concentration
CR	Complete response
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CT	Computed tomography
CTCAE v5.0	Common Terminology Criteria for Adverse Events Version 5.0
C_{trough}	The concentration observed immediately before next dosing (corresponding to pre dose or trough concentration for multiple dosing)
DNA	Deoxyribonucleic acid
DOR	Duration of response
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic Case Report Form
EGFR	Epidermal growth factor receptor
CCI [redacted]	
EoT	End of Treatment
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
GCP	Good Clinical Practice

HBV	Hepatitis B virus
HCV	Hepatitis C virus
IAP	Integrated Analysis Plan
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IRB	Institutional Review Board
iv	Intravenous
irAE	Immune-related adverse event
CCI [redacted]	
CCI [redacted]	
CCI [redacted]	
CCI [redacted]	
CCI [redacted]	
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD	Progression of disease
PD-1	Programmed cell death protein-1
PD-L1	Programmed death ligand 1
PFS	Progression-free survival
CCI [redacted]	
PK	Pharmacokinetics
PR	Partial response
CCI [redacted]	
RECIST v1.1	Response evaluation criteria in solid tumors version 1.1

RNA	Ribonucleic acid
SAE	Serious adverse event
CCI	[redacted]
SMC	Safety Monitoring Committee
SmPC	Summary of product characteristics
TEAE	Treatment-emergent adverse event
TMTB	Total measured tumor burden
ULN	Upper limit of normal
WOCBP	Woman of childbearing potential

Appendix 2 Study Governance

Financial Disclosure

Investigators and Sub-Investigators will provide the Sponsor with sufficient, accurate financial information, as requested, for the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. This information is required during the study and for 1 year after completion of the study.

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions on the study.
- Participants must be informed that their participation is voluntary.
- Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50; local regulations; ICH guidelines; Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable; and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- If the ICF is updated during their participation in the study, participants must be re-consented to the most current, approved version.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- The original signed and dated consent will remain at the Investigator's site and must be safely archived so that it can be retrieved at any time for monitoring, auditing and inspection purposes.

Data Protection

- The Sponsor will assign a unique identifier to participants after obtaining their informed consent. All participant records or datasets transferred to the Sponsor will contain the identifier only; participant names or any identifiable information will not be transferred.
- The Sponsor must inform participants that their personal study-related data will be used per local data protection and privacy laws. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other Sponsor-appointed, authorized personnel, by appropriate IRB/IEC members, and by regulatory authority inspectors. All such persons will strictly maintain participants' confidentiality.

Participant's rights under data protection laws:

- Participant may use his/her rights under his/her applicable data protection laws to access and correct his/her personal information, ask for it to be deleted, to have it transferred in a common electronic format to another study center or to object to sharing de-identified data for other research purposes
- However, if and to the extent his/her request may inhibit the further conducting of the study or the sharing of data for research purposes the request may be rejected according to applicable laws
- Participant can also request a copy of data transfer clauses if his/her personal data is shared outside the EU. Participant should contact the study center (where applicable: or its data protection officer) in case he/she want to make use of his/her rights under data protection laws. Participant may also contact his/her data protection authority if she/he has any concerns about handling of his/her personal data.

Study Administrative

The Sponsor of this clinical study is Merck KGaA, Darmstadt, Germany.

The study will be conducted in approximately 25 clinical centers in Europe.

The Coordinating Investigator listed on the title page represents all Investigators for decisions and discussions on this study, per ICH GCP. The Coordinating Investigator will provide expert medical input and advice on the study design and execution and is responsible for the review and signoff of the clinical study report.

The study will appear in the following clinical studies registries: Clinicaltrials.gov, EudraCT. As per company policy study will be published approximately 2 weeks prior to first patient-in. Therefore NCT number from Clinicaltrials.gov cannot been provided before that point in time.

A Safety Monitoring Committee (SMC), consisting of permanent members from the Sponsor and CRO, the Coordinating Investigator, and other optional members with expertise in the management of cancer subjects, will review the safety data on a regular basis throughout the trial. The SMC will decide by consensus on the continuation or suspension of enrollment after an initial safety run-in of cetuximab in combination with avelumab plus gemcitabine and cisplatin and will review all available safety data. The specific working procedures will be described in an SMC charter, which will be established prior to the start of recruitment.

A contract research organization, PPD , will undertake the operational aspects of this study. Details of such structures and associated procedures will be defined in a separate Integrated Project Management Plan (IPMP) maintained by PPD . The IPMP will be prepared by the PPD Clinical Project Manager in cooperation with other PPD Operational Team Leads.

The Clinical Study Supplies department of the Sponsor will supply the study medication of avelumab and as applicable placebo and/or comparator treatment(s). Clinical supply is performed by the Clinical Trial Supply function of the Sponsor.

The Global Patient Safety Department, Merck KGaA, Darmstadt, Germany, or their designated representatives will supervise drug safety and the timely reporting of adverse events (AEs) and Serious Adverse Events (SAEs).

Quality assurance of the study conduct will be performed by the Development Quality Assurance Department, Merck KGaA, Darmstadt, Germany.

The department of Global Biostatistics will supervise the statistical analyses (with the exception of the PK data analyses), which will be outsourced to a CRO.

Details of structures and associated procedures will be defined in a separate Study Reference Manual, which will be prepared under the supervision of the Clinical Study Leader.

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and the following:
    - Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable ICH Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations.
- The Investigator must submit the protocol, protocol amendments (if applicable), ICF, Investigator Brochure, and other relevant documents (for example, advertisements) to an IRB/IEC and the IRB/IEC must review and approve them before the study is initiated.
- Any protocol amendments (ie, changes to the protocol) will be documented in writing and require IRB/IEC approval before implementation of changes, except for changes necessary to eliminate an immediate hazard to study participants. When applicable, amendments will be submitted to the appropriate Health Authorities.
- The Investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently per the IRB's/IEC's requirements, policies, and procedures.
    - Notifying the IRB/IEC of SAEs or other significant safety findings, as required by IRB/IEC procedures.
    - Providing oversight of the study conduct at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.
- The protocol and any applicable documentation will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each site.

Emergency Medical Support

- The Sponsor or designee will provide Emergency Medical Support cards to participants for use during the study. These provide the means for participants to identify themselves as

participating in a clinical study. Also, these give health care providers access to any information about this participation that may be needed to determine the course of medical treatment for the participant. The information on the Emergency Medical Support card may include the process for emergency unblinding (if applicable).

- The first point of contact for all emergencies will be the clinical study Investigator caring for the participant. Consequently, the Investigator agrees to provide his or her emergency contact information on the card. If the Investigator is available when an event occurs, they will answer any questions. Any subsequent action (for example, unblinding) will follow the standard process established for Investigators.

  When the Investigator is not available, the Sponsor provides the appropriate means to contact a Sponsor physician. This includes provision of a 24-hour contact number at a call center, whereby the health care providers will be given access to the appropriate Sponsor physician to assist with the medical emergency and to provide support for the potential unblinding of the participant concerned.

Clinical Study Insurance and Compensation to Participants

Insurance coverage will be provided for each country participating in the study. Insurance conditions shall meet good local standards, as applicable.

Clinical Study Report

After study completion, the Sponsor will write a clinical study report in consultation with the Coordinating Investigator and any Steering Committee or other relevant study-appointed committees or groups.

Publication

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows Merck to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. Per standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a Coordinating Investigator will be designated by agreement.
- Authorship will be determined by agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

- Posting of data on Clinicaltrials.gov, EudraCT, and all other required registries is planned and will occur 12 months after the last clinic visit of the final study participant or another appropriate date to meet applicable requirements.
- A CSR will be written within 12 months after the last clinic visit of the final study participant or another appropriate date to meet applicable requirements. The CSR will be distributed in accordance to EU 536/2014 and all other applicable regulations. Clinical sites, IRBs and local

authorities will receive the CSR synopsis, except the full CSR is requested by national regulations. This includes access to CSRs from studies with negative outcomes and from terminated development programs.

- Periodic Safety Reports, and clinical study summary reports will be submitted according to national regulations that need to be followed.

Data Quality Assurance

- All participant study data will be recorded on printed or electronic CRFs or transmitted to the Sponsor or designee electronically (for example, laboratory data). The Investigator is responsible for verifying that data entries are complete, accurate, legible, and timely by physically or electronically signing the CRF. Details for managing CRFs are in the Study Reference Manual.
- The Investigator must maintain accurate documentation (source data) that supports the information in the CRF.
- The Investigator must permit study-related monitoring, quality assurance audits, IRB/IEC review, and regulatory agency inspections and provide direct access to the study file and source data.
- The Sponsor or designee is responsible for data management of this study, including quality checking of the data and maintaining a validated database. Database lock will occur once quality control and quality assurance procedures have been completed. PDF files of the CRFs will be provided to the Investigators at study completion.
- Study monitors will perform ongoing source data verification to confirm that data in the CRF are accurate, complete, and verifiable; that the safety and rights of participants are being protected; and that the study is being conducted per the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion, unless local regulations, institutional policies, or the Sponsor requires a longer retention. No records may be destroyed during the retention period without the Sponsor's written approval. No records may be transferred to another location or party without the Sponsor's written notification.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected.
- The Investigator must keep a paper or electronic file (medical file and original medical records) at the site for each study participant. The file must identify each participant, contain the following demographic and medical information for the participant, and should be as complete as possible:
    - Participant's full name, date of birth, sex, height, and weight
    - Medical history and concomitant diseases
    - Prior and concomitant therapies (including changes during the study)

- Study identifier (ie, the Sponsor's study number) and participant's study number
- Dates of entry into the study (ie, signature date on the informed consent) and each visit to the site
- Any medical examinations and clinical findings predefined in the protocol
- All AEs
- Date that the participant left the study, including any reason for early withdrawal from the study or study intervention, if applicable.

- All source data must be filed (for example, CT or MRI scan images, ECG recordings, and laboratory results). Each document must have the participant number and the procedure date; ideally, printed by the instrument used for the procedure. As necessary, medical evaluation of these records should be performed, documented, signed and dated by the Investigator.
- Data recorded on printed or electronic CRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- The study monitors will use printouts of electronic files for source data verification. These printouts must be signed and dated by the Investigator, countersigned by the Monitor and kept in the study file.
- Source documents are stored at the site for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. The Investigator ensures that no destruction of medical records is performed without the Sponsor's written approval.
- Definition of what constitutes source data is found in Source Data Identification Log.

Study and Site Closure

- The Sponsor reserves the right to close the study site or terminate the study at any time and for any reason. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a site closure visit has been completed.
- The Investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.
- Reasons for the early closure of a study site by the Sponsor or Investigator may include:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local Health Authorities, the Sponsor's procedures, or GCP guidelines
  - Inadequate recruitment of participants by the Investigator
  - Discontinuation of further development of the Sponsor's compound.

Appendix 3 Contraception

Woman of Childbearing Potential (WOCBP)

A woman is of childbearing potential (ie, fertile), following menarche and until either:

1) Becoming postmenopausal; or,
2) is permanently sterile by means of a hysterectomy, bilateral salpingectomy or bilateral oophorectomy.

Postmenopausal is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Highly Effective Contraceptive Methods

Highly effective methods are those with a failure rate of less than 1% per year when used consistently and correctly.

These methods are further classified into user-independent and user-dependent methods. Because user-independent methods do not depend on the participant's ability to use them consistently and correctly, they are preferred when contraception is introduced as a condition for study participation.

Caution should be taken for hormonal contraception, as it may be susceptible to interaction with the study intervention(s), which may reduce the efficacy of the contraception method. In this case, a second highly effective method of contraception should be used during the treatment period and for at least 60 days after the last dose of study treatment.

User-Dependent

- 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.

User-Independent

- Implantable progestogen-only hormonal contraception associated with inhibition of ovulation
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)

- Bilateral tubal occlusion
- Vasectomized partner: This is a highly effective contraception method only if the partner is the sole sexual partner of the WOCBP and he has received medical assessment of the surgical success.
- Sexual abstinence: This is a highly effective method only if the WOCBP refrains from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Acceptable Contraceptive Method

Allowed only under certain situations, as specified in the CTFG recommendations, because they have a failure rate of **more than** 1% per year and therefore are not considered to be highly effective methods.

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide
- Cap, diaphragm or sponge with spermicide
- Combination of a male condom with cap, diaphragm or sponge with spermicide (ie, double barrier method).

Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definitions

Adverse Event

An AE is any untoward medical occurrence in a participant administered a pharmaceutical product, regardless of causal relationship with this treatment. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, regardless if it is considered related to the medicinal product.

For surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

The Investigator is required to grade the severity or toxicity of each AE.

Investigators will reference the National Cancer Institute - Common Terminology Criteria for AEs (CTCAE), version 5.0 (publication date: 27 Nov 2017), a descriptive terminology that can be used for AE reporting.

A general grading (severity/intensity; hereafter referred to as severity) scale is provided at the beginning of the above referenced document, and specific event grades are also provided.

If the severity for an AE is not specifically graded by NCI-CTCAE, the Investigator is to use the general NCI-CTCAE definitions of Grade 1 through Grade 5, using his or her best medical judgment.

The 5 general grades are:

Grade 1 or Mild

Grade 2 or Moderate

Grade 3 or Severe

Grade 4 or Life-threatening

Grade 5 or Death

Any clinical AE with severity of Grade 4 or 5 must also be reported as an SAE. However, a laboratory abnormality of Grade 4, such as anemia or neutropenia, is considered serious only if the condition meets one of the serious criteria specified below.

If death occurs, the primary cause of death or event leading to death should be recorded and reported as an SAE. "Fatal" will be recorded as the outcome of this specific event and death will

not be recorded as separate event. Only, if no cause of death can be reported (for example, sudden death, unexplained death), the death per se might then be reported as an SAE.

Investigators must also systematically assess the causal relationship of AEs to study intervention (including any other non-study interventions, radiation therapy, etc.) using the following definitions. Decisive factors for the assessment of causal relationship of an AE to the study interventions include, but may not be limited to, temporal relationship between the AE and the study interventions, known side effects of the study interventions, medical history, concomitant medication, course of the underlying disease, and study procedures.

Unrelated: Not reasonably related to the study intervention. AE could not medically (pharmacologically/clinically) be attributed to the study intervention under study in this clinical study protocol. A reasonable alternative explanation must be available.

Related: Reasonably related to the study intervention. AE could medically (pharmacologically/clinically) be attributed to the study intervention under study in this clinical study protocol.

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

Abnormal laboratory findings and other abnormal investigational findings (for example, on an ECG trace) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to study intervention discontinuation or are considered otherwise medically important by the Investigator. If a laboratory abnormality fulfills these criteria, the identified medical condition (for example, anemia or increased ALT) must be reported as the AE rather than the abnormal value itself.

Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening. Life-threatening refers to an event in which the participant is at risk of death at the time of the event, not an event that hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongs an existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is otherwise considered to be medically important. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the participant or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For the purposes of reporting, any suspected transmission of an infectious agent via a study intervention is also considered an SAE, as specified below for reporting SAEs and AESIs.

Events that Do Not Meet the Definition of an SAE

Elective hospitalizations to administer, or to simplify study intervention or procedures (for example, an overnight stay to facilitate chemotherapy and related hydration therapy application) are not considered SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (ie, undesirable effects of any administered treatment) must be documented and reported as SAEs.

Events Not to Be Considered as AEs/SAEs

Medical conditions present at the initial study visit that do not worsen in severity or frequency during the study are defined as Baseline Medical Conditions, and are not to be considered AEs.

AE/SAEs Observed in Association with Disease Progression

Progression of the disease/disorder being studied assessed by measurement of lesions on radiographs or other methods as well as associated clinical signs or symptoms (including laboratory abnormalities) should not be reported as an (S)AE, unless the patient's general condition is more severe than expected for the participant's condition and/or unless the outcome is fatal within the adverse event reporting period, as defined in Section 8.3.2 (Method of Detecting Adverse Events and Serious Adverse Events)

Adverse Events of Special Interest (AESI)

Infusion-related reactions including drug hypersensitivity reactions and immune-mediated adverse reactions (immune-related pneumonitis, immune-related colitis, immune-related hepatitis, immune-related endocrinopathies (thyroid disorders, adrenal insufficiency, new onset type I diabetes mellitus, pituitary disorders), immune-related nephritis and renal dysfunction and other immune-related AEs (myositis, myocarditis, Guillain-Barré syndrome, uveitis) have been identified as adverse events of special interest for avelumab. Any AE that is suspected to be a potential immune-mediated adverse reaction or infusion-related reaction will be considered an adverse event of special interest (AESI).

These AESI do not require expedited reporting unless they are serious. Should the AESI be serious, a SAE form should be filled instead and the reporting process for SAEs should be followed. Additional information on AESIs are in the avelumab and cetuximab IBs.

There are no specified AESI for cetuximab.

Recording and Follow-up of AE and/or SAE

It is important that each AE report include a description of the event, its duration (onset and resolution dates and also onset and resolution times, when it is important to assess the time of AE onset relative to the recorded study intervention administration time), its severity, its causal relationship with the study intervention, any other potential causal factors, any treatment given or

other action taken, including dose modification or discontinuation of the study intervention, and its outcome. In addition, serious cases should be identified and the appropriate seriousness criteria documented.

Specific guidance is in the CRF Completion and Monitoring Conventions provided by the Sponsor.

Reporting Serious Adverse Events and Adverse Events of Special Interest

Serious Adverse Events

In the event of any new SAE occurring during the reporting period, the Investigator must immediately (within a maximum of 24 HOURS after becoming aware of the event) inform the Sponsor or its designee in writing. All written reports should be transmitted using the SAE Report Form, which must be completed by the Investigator following specific completion instructions.

In exceptional circumstances, an SAE (or follow-up information) may be reported by telephone; in these cases, a written report must be sent immediately thereafter by fax or e-mail. Names, addresses, and telephone and fax numbers for SAE reporting will be included in the study specific SAE Report Form.

Relevant pages from the CRF may be provided in parallel (for example, medical history, concomitant drugs). Additional documents may be provided by the Investigator, if available (for example, laboratory results, hospital report, autopsy report). In all cases, the information provided on the SAE Report Form must be consistent with the data about the event recorded in the CRF.

The Investigator must respond to any request for follow-up information (for example, additional information, outcome, final evaluation, other records where needed) or to any question the Sponsor/designee may have on the AE within the same timelines as those noted above for initial reports. This is necessary to ensure prompt assessment of the event by the Sponsor or designee and (as applicable) to allow the Sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations.

Requests for follow-up will usually be made via the responsible Monitor, although in exceptional circumstances the drug safety department may contact the Investigator directly to obtain further information or to discuss the event.

Adverse Events of Special Interest

In the event of a non-serious AESI, the Investigator will complete the AESI Report Form and send it to the Sponsor/designee within a maximum of 24 HOURS after becoming aware of the event. Names, addresses, and telephone and fax numbers for AESI reporting will be included on the Report Form. Serious AESIs must be reported in an expedited manner as SAEs as outlined above.

Appendix 5 Liver Safety: Suggested Actions and Follow-up Assessments

See Section 6.9.1 for details on management of liver irAEs.

Appendix 6 Clinical Laboratory Tests

Table 18 Protocol-Required Clinical Laboratory Assessments

Full Chemistry	Core Chemistry[a]	Hematology
Albumin	Alkaline phosphatase	Absolute lymphocyte count
Alkaline phosphatase	ALT	Absolute neutrophil count
ALT	AST	Hematocrit
Amylase	BUN/total urea	Hemoglobin
AST	Calcium	Platelet count
GGT	Chloride	RBC count
BUN/total urea	Creatinine	White blood cell count and differential count
Calcium	Glucose	
Chloride	Phosphorus/Phosphates	
Cholesterol	Magnesium	
Creatine kinase	Potassium	
Creatinine	Sodium	
CRP	Total bilirubin	
Glucose	Lipase	**Hemostaseology**
LDH	Amylase	aPTT
Lipase	Creatine kinase	Prothrombin time/INR
Phosphorus/Phosphates		
Magnesium		**Basic Urinalysis** (dipstick, including macroscopic appearance, bilirubin, blood, color, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen) Full urinalysis (dipstick plus microscopic evaluation) to be performed only at the Screening and End of Treatment visit.
Potassium		
Sodium		
Total bilirubin		
Total protein		
Uric acid		Totality of binding ADA
Triglycerides		
		TSH, and T4
Hormone		
FSH		

ADA = antidrug antibody, ALT = alanine aminotransferase, aPTT = activated partial thromboplastin time, AST = aspartate aminotransferase, BUN= blood urea nitrogen, CRP = C-reactive protein, FSH = follicle stimulating hormone, GGT = gamma-glutamyltransferase, INR = international normalized ratio, LDH = lactate dehydrogenase, RBC = red blood cell, TSH = thyroid stimulating hormone, T4 = free thyroxine.

[a] Core serum chemistries.

Appendix 7 Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Not applicable.

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

Appendix 10 Protocol Amendment History

The information for the current amendment is on the title page.

Appendix 11 Sponsor Signature Page

Study Title:	A Phase IIa, single-arm, multicenter study to investigate the clinical activity and safety of avelumab in combination with cetuximab plus gemcitabine and cisplatin in participants with advanced squamous non-small-cell lung cancer
Regulatory Agency Identifying Numbers:	EudraCT number: 2018-001529-24 ClinicalTrials.gov: NCT03717155
Clinical Study Protocol Version:	20 August 2019/Version 2.0

I approve the design of the clinical study:

PPD

Signature

PPD

Date of Signature

Name, academic degree:	PPD
Function/Title:	PPD
Institution:	Merck KGaA
Address:	Frankfurter Strasse 250 64293 Darmstadt, Germany
Telephone number:	PPD
Fax number:	PPD
E-mail address:	PPD

Appendix 12 Coordinating Investigator Signature Page

Study Title:	A Phase IIa, single-arm, multicenter study to investigate the clinical activity and safety of avelumab in combination with cetuximab plus gemcitabine and cisplatin in participants with advanced squamous non-small-cell lung cancer
Regulatory Agency Identifying Numbers:	EudraCT number: 2018-001529-24 ClinicalTrials.gov: NCT03717155
Clinical Study Protocol Version:	20 August 2019/Version 2.0
Site Number:	

I approve the design of the clinical study, am responsible for the conduct of the study at this site, and understand and will conduct it per the clinical study protocol, any approved protocol amendments, International Council for Harmonization Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

PPD

Signature

PPD

Date of Signature

Name, academic degree:	PPD
Function/Title:	PPD
Institution:	PPD
Address:	PPD
Telephone number:	PPD
Fax number:	PPD
E-mail address:	PPD

Appendix 13 Principal Investigator Signature Page

Study Title:	A Phase IIa, single-arm, multicenter study to investigate the clinical activity and safety of avelumab in combination with cetuximab plus gemcitabine and cisplatin in participants with advanced squamous non-small-cell lung cancer
Regulatory Agency Identifying Numbers:	EudraCT number: 2018-001529-24 ClinicalTrials.gov: NCT03717155
Clinical Study Protocol Version:	20 August 2019/Version 2.0
Site Number:	

I am responsible for the conduct of the study at this site and understand and will conduct it per the clinical study protocol, any approved protocol amendments, International Council for Harmonization Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

_____ _____

Signature Date of Signature

Name, academic degree:

Function/Title:

Institution:

Address:

Telephone number:

Fax number:

E-mail address: