CLINICAL STUDY PROTOCOL

OPEN LABEL, MULTICENTER PHASE II STUDY OF THE C5A-ANTIBODY IFX-1 ALONE OR IFX-1 + PEMBROLIZUMAB IN PATIENTS WITH PD-1- OR PD-L1-RESISTANT/REFRACTORY LOCALLY ADVANCED OR METASTATIC CUTANEOUS SQUAMOUS CELL CARCINOMA (CSCC)

Protocol Number:	IFX-1-P2.8
Compound:	IFX-1
Phase:	II
Indication:	Locally advanced or metastatic cutaneous squamous cell carcinoma (cSCC)
IND Number: EudraCT Number:	144632 2020-000864-42
Sponsor Name and Address:	InflaRx GmbH Winzerlaer Strasse 2 07745 Jena, Germany
Version and Date:	Version 4.0, 12 May 2021

PROTOCOL SIGNATURES

Sponsor Signatory

Protocol Number: IFX-1-P2.8

Title: Open label, multicenter phase II study of the C5a antibody IFX-1 alone or IFX-1 + pembrolizumab in patients with PD-1 or PD-L1 resistant/refractory locally advanced or metastatic cutaneous squamous cell carcinoma (cSCC)

[redacted]

01-JUN-2021

Date

[redacted]

Clinical Research and Development

Medical monitor name and contact information will be provided separately.

Biostatistician

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[redacted]

28-May-202

Date

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Biostatistician
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Signature of National Coordinating Investigator (if applicable)

Protocol Number: IFX-1-P2.8

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Date **Name:**

_____

National Coordinating Investigator

Investigator Protocol Signature Page

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I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated, in accordance with all stipulations of the protocol and in accordance with Good Clinical Practice, local regulatory requirements, and the Declaration of Helsinki.

Date	**Name:**
	_____
	Principal Investigator

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ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	Antidrug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
C5aR	C5a receptor
CFR	Code of Federal Regulations
C_{max}	Peak concentrations
CR	Complete response
cSCC	Cutaneous squamous cell carcinoma
CT	Computed tomography
C_{trough}	Trough concentrations
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
eCRF	Electronic case report form
EORTC	European Organisation for Research and Treatment of Cancer
EOS	End of study
EOT	End of treatment
FAS	Full analyses set
FDG	Fluorodeoxyglucose
H0	Beginning of IFX-1 administration
HS	Hidradenitis suppurativa
IB	Investigator Brochure
iCPD	Confirmed progressive disease
iCR	Complete response according to iRECIST
IEC	Independent Ethic Committee
IgG4	Immunoglobulin G4
IL	Interleukin
IMP	Investigational medicinal product
IND	Investigational new drug
iPR	Partial response according to iRECIST
irAE	Immune related- adverse event
IRB	Independent Review Board

iRECIST	Response evaluation criteria in solid tumors for immune-based therapeutics
iSD	Stable disease according to iRECIST
iUPD	Unconfirmed progressive disease according to iRECIST
IWRS	Interactive Web Response System
Km	Michaelis constant (substrate concentration at which the reaction rate is half of its maximal value; indicates the affinity of an enzyme for a given substrate)
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute common terminology criteria for adverse events
NMSC	Non-melanoma skin cancer
NOAEL	No Observed Adverse Effect Level (Highest dose at which there is no toxic or adverse effect observed)
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed cell death 1 protein
PD-L1(2)	Programmed cell death ligand 1 (2)
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetic
PR	Partial response
Q2W	Bi-weekly
Q3W	Every 3 weeks
Q4W	Every 4 weeks
Q6W	Every 6 weeks
QLQ	Quality of life questionnaire
QoL	Quality of life
QW	Weekly
RECIST	Response evaluation criteria in solid tumors
RNA	Ribonucleic acid

RP2D	Recommended Phase II dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SCC	Squamous cell carcinoma
SD	Stable disease
SoA	Schedule of assessments
TEAE	Treatment-emergent adverse event
TME	Tumor microenvironment
ULN	Upper limit of normal
UV	Ultraviolet
uPA	Urokinase plasminogen activator
WHO	World Health Organization
WOCBP	Women of childbearing potential

1. SYNOPSIS

Title of Study:

Open label, multicenter Phase II study of the C5a-antibody IFX-1 alone or IFX-1 + pembrolizumab in patients with PD-1- or PD-L1-resistant/refractory locally advanced or metastatic cutaneous squamous cell carcinoma (cSCC)

Protocol/Study Number: IFX-1-P2.8

EudraCT Number: 2020-000864-42

Type of Study:	**Indication:**
Proof of Concept Study	Locally advanced or metastatic cutaneous squamous cell carcinoma (cSCC)

Sponsor: InflaRx GmbH, Winzerlaer Strasse 2, 07745 Jena, Germany

Study Site(s):

Approximately 32 sites in approximately 6 countries

Phase of Development: II

Objectives:

Primary Objectives:

Arm A:

- To assess the antitumor activity of IFX-1

Arm B:

- To determine the maximum tolerated dose (MTD) or recommended Phase II dose (RP2D)
- To assess the antitumor activity of IFX-1 + pembrolizumab
- To assess the safety profile of IFX-1 + pembrolizumab

Secondary Objectives:

Arm A:

- To further assess efficacy of IFX-1
- To assess the safety profile of IFX-1
- To assess the pharmacokinetics (PK) of IFX-1
- To monitor the immunogenicity of IFX-1
- To assess the impact of IFX-1 on quality of life (QoL)

Arm B:

- To further assess efficacy of IFX-1
- To assess the PK of IFX-1

- To monitor the immunogenicity of IFX-1
- To assess the impact of IFX-1 + pembrolizumab on QoL

Methodology:

This is an open-label, non-randomized, Phase II study. Patients will be enrolled in 2 treatment arms (Arm A: IFX-1 monotherapy; Arm B: IFX-1 + pembrolizumab combination therapy), both consisting of 2 stages. Enrollment follows an optimal Simon's 2-stage design with an interim analysis of treatment response after Stage 1 prior to patient enrollment into Stage 2.

Arm B will start after ≥3 patients have been treated in Arm A and no toxicity concerns have emerged. In a safety run-in part of Arm B with 3 dose cohorts, escalating doses of IFX-1 will be investigated in combination with 400 mg pembrolizumab every 6 weeks [Q6W], in order to identify the MTD or RP2D. The MTD or RP2D will be explored in a Phase II portion of Arm B. Patients will be treated until progression, occurrence of unacceptable toxicity, or treatment discontinuation for any other reason.

Number of Patients:

Up to approximately 70 patients

Study Population:

Patients must meet all the following criteria at screening and at inclusion to participate in the study:

1. At least 18 years of age on day of signing informed consent
2. Patients with biopsy-proven, histologically or cytologically confirmed (a.) locally advanced cSCC not amenable for curative treatment or (b.) metastatic cSCC. Patients must have been treated with all approved therapies for (a.) inoperable locally advanced cSCC contraindicated for radiation therapy or (b.) metastatic cSCC.

   Note: More details defining eligibility of locally advanced cSCC or metastatic cSCC can be found in the body text.
3. Patients must have progressed on treatment with an anti-PD1/L1 monoclonal antibody (mAb) administered either as monotherapy or in combination with other checkpoint inhibitors or other therapies. PD-1 treatment progression is defined by meeting all of the following criteria:

   a) Has received ≥2 doses of an anti-PD1/L1 mAb that has been approved for treatment of cSCC or any solid tumor

   b) Has demonstrated progressive disease (PD)/confirmed PD (iCPD) after PD-1/L1 inhibitor treatment as defined by modified response evaluation criteria in solid tumors (RECIST) version 1.1/RECIST for immune-based therapeutics (iRECIST). The initial evidence of PD is to be confirmed by a second assessment

≥4 weeks from the date of the first documented PD, unless there is rapid clinical progression.

c) Disease progression has been documented within 12 weeks from the last dose of anti-PD-1/L1 mAb.

4. The PD-1-/PDL1 infusion must have been the most recent treatment for locally advanced or metastatic cSCC.
5. Patients must consent to undergo the following biopsies (at each time point a punch biopsy of externally visible cSCC lesions or a biopsy of material from accessible metastases) for biomarker assessments:

   a. At baseline, prior to the first administration of the investigational therapy and if possible, within 7 days prior to initiation of study treatment administration (mandatory for all patients)
   b. For Stage 2 patients only: on Cycle 2 Day 1 (±3 days) (mandatory)
   c. For Stage 2 patients only: at the time of CR/iCR/PR/iPR (optional, to be conducted only if the investigator considers this biopsy as clinically possible and potentially informative)
   d. For Stage 2 patients only: At the time of tumor progression (optional, to be conducted only if the investigator considers this biopsy as clinically possible and potentially informative).

   For all biopsies intended to analyze biomarkers, it is important to obtain sufficient material to conduct the biomarker program, which needs to be the equivalent to a 4 mm x 4 mm punch biopsy. If biopsies for biomarkers are not feasible due to the complete absence of any suitable cutaneous or metastatic lesions, then this is not an exclusion criterium. However, this needs to be documented and confirmed by the investigator.

   The biopsied lesion is not considered a target lesion.

6. Patients must have the following minimum washout before first study treatment administration from previous treatments:

   - ≥4 weeks for mAbs, systemic cytotoxic anticancer therapy, treatment with other anticancer investigational agents
   - ≥3 weeks for local radiation therapy

   Note: Patients must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-central nervous system disease.

7. Eastern Cooperative Oncology Group performance status (ECOG PS) status of ≤1

   Adequate organ function:

System	Laboratory Value
Hematological	
Absolute neutrophil count	≥1 500/µL
Platelets	≥100 000/µL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Creatinine OR Measured or calculated[b] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥30 mL/min for patient with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for patients with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for patients with liver metastases)
Coagulation	
International normalized ratio OR PT aPTT	≤1.5 × ULN unless patient is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); aPTT=activated partial thromboplastin time; AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); CrCL=creatinine clearance; GFR=glomerular filtration rate; PT=prothrombin time; ULN=upper limit of normal.

a Note hematology test should be obtained without transfusion or receipt of stimulating factors within 2 weeks before obtaining screening blood sample.:
b CrCl should be calculated per institutional standard.

8. Patient (or legally acceptable representative if applicable) provides written informed consent for the study.

Patients who fulfil any of the following criteria at screening are not eligible to participate in the study:

1. Patients with limited cSCC, who do not require systemic therapy

2. Has known active central nervous system metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided they are

radiologically stable, i.e., without evidence of progression for ≥4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable, and without requirement of steroid treatment for ≥14 days prior to first dose of study treatment.

3. Has a diagnosis of immunodeficiency or autoimmune disease, or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 3 weeks prior the first dose of study treatment

4. Patients who have a history of (non-infectious) pneumonitis that required steroids or have current pneumonitis

5. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent, or with an agent directed to another stimulatory or co-inhibitory T cell receptor (e.g., cytotoxic -T-lymphocyte-associated antigen 4, OX 40, CD137) and was discontinued from that treatment due to a ≥Grade 3 immune-related adverse event (irAE)

6. Has severe hypersensitivity (≥Grade 3) to pembrolizumab or IFX-1 and/or any of their excipients or had a severe (≥Grade 3) infusion-related reaction to treatments with other mAbs

7. Patients who fulfil inclusion criterion 6 (washout times) but who have not recovered from side effects of such therapies

8. Has received a live vaccine within 30 days prior to the first dose of study treatment

9. Patients who have undergone major surgery <4 weeks prior to starting study treatment

10. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study treatment

    Note: Patients who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks after the last dose of the previous investigational agent.

11. Patients with known ≥Grade 3 (per National Cancer Institute common terminology criteria for adverse events [NCI CTCAE] v5.0 criteria) active systemic or cutaneous viral, bacterial, or fungal infection

12. Patients with known history of Hepatitis B or C infections or known to be positive for Hepatitis B antigen (HBsAg)/ Hepatitis B virus (HBV) DNA or Hepatitis C Antibody or RNA.

13. Patients who have a history of human immunodeficiency virus infection

14. Patients who have a history of interstitial lung disease

15. Patients who have had an allogeneic tissue/solid organ transplant

16. Patients with a history of other malignancies during the past 5 years. Note: The following are exempt from the 5-year limit: curatively resected basal cell carcinoma, or carcinoma in situ (e.g., breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy.

17. Patients who are pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through [redacted] after the last dose of IFX-1 or 120 days after the last dose of pembrolizumab

18. Women of childbearing potential (WOCBP) who have a positive serum pregnancy test result within 7 days before treatment. Note: Post-menopausal women must be amenorrheic for ≥12 months to be considered not WOCBP.

19. Male patients and WOCBP who do not agree to practice an effective method of contraception during study and [redacted] after last dose of IFX-1 or 120 days after last dose of pembrolizumab

20. Patients with congestive heart failure, Class III or IV, by New York Heart Association criteria

21. Patients with any serious underlying medical condition that would impair their ability to receive or tolerate the planned treatment

22. Patients with dementia or altered mental status that would preclude understanding and rendering of informed consent document

Test Product, Dose, and Mode of Administration:

In treatment Arm A, IFX-1 monotherapy will be administered as a 30-minute (-5/+10 minutes) intravenous infusion as follows: 800 mg on Days 1, 4, 8, and 15, followed by 1600 mg Q2W starting on Day 22 of Cycle 1 until end of treatment (EOT).

In treatment Arm B, IFX-1 will be administered as a 30-minute (-5/+10 minutes) intravenous infusion as follows: 400 mg (regimen 1), 600 mg (regimen 2), or 800 mg (regimen 3) on Days 1, 4, 8, and 15, followed by 800 mg Q2W (regimen 1), 1200 mg Q2W (regimen 2), or 1600 mg Q2W (regimen 3) starting on Day 22 of Cycle 1 until EOT. IFX-1 treatment will be combined with pembrolizumab, administered as a 30-minute (-5/+10 minutes) intravenous infusion at a dose of 400 mg starting at Day 8 of Cycle 1 and then Q6W on Day 1 of each treatment cycle. IFX-1 infusion will start 60 minutes (±10 minutes) after the pembrolizumab-infusion has been finished.

For those patients receiving less than 1600 mg IFX-1 Q2W (regimen 1 and 2) the dose of IFX-1 may be increased to 1600 mg Q2W at the discretion of the investigator and after consultation

with the sponsor as soon as the safety of this dose will have been confirmed in at least 3 patients receiving 1600 mg Q2W (regimen 3).

Treatment will be continued until either disease progression is diagnosed, unacceptable toxicity occurred, or treatment has been administered for approximately 2 years.

Reference Therapy, Dose, and Mode of Administration:

NA

Study Duration:

The expected duration of the study from "first patient first visit" to "last patient last follow-up visit" is 3 years.

Criteria for Evaluation

Primary Endpoint:

Arm A:

- Investigator assessed best overall response rate (ORR) for IFX-1, with response being defined as best response of CR/confirmed CR (iCR) or PR/confirmed PR (iPR) per modified RECIST v1.1/iRECIST

Arm B:

- Frequency of dose-limiting toxicities (DLTs) by dose cohort
- Investigator assessed best ORR for IFX-1 + pembrolizumab, with response being defined as best response of CR/confirmed CR (iCR) or PR/confirmed PR (iPR) per modified RECIST v1.1/iRECIST
- Frequency, severity, and investigational new drug (IND) attribution of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) according to Medical Dictionary for Regulatory Activities (MedDRA) coding (version valid at time of reporting) and the NCI CTCAE grading system (version 5.0, 27 November 2017)

Secondary Endpoints:

Arm A:

- Response (CR/iCR/PR/iPR) and stable disease (SD) duration
- Disease control rate (CR/iCR+PR/iPR+SD)
- Progression-free survival (PFS)
- Overall survival (OS)
- Frequency, severity, and IND attribution of TEAEs and SAEs according to MedDRA coding (version valid at time of reporting) and the NCI CTCAE grading system v5.0
- Post infusion maximum (C_{max}) and trough concentration (C_{trough}) of IFX-1
- Development of human antidrug antibodies (ADAs) against IFX-1

- Changes in QoL as per the European Organisation for Research and Treatment of Cancer (EORTC)-QoL questionnaire (QLQ)-C30 total score

Arm B:

- Response (CR/iCR/PR/iPR) and SD duration
- Disease control rate (CR/iCR+PR/iPR+SD)
- PFS
- OS
- C_{max}, and C_{trough} of IFX-1
- Development of human ADAs against IFX-1
- Changes in QoL as per the EORTC-QLQ-C30 total score

Statistical Methods:

Efficacy: All efficacy analyses will be performed on the full analysis set. All analyses will be conducted separately by treatment arm. Patients will be analyzed descriptively and stratified by locally advanced or metastatic cSCC. The 2 treatment arms will be compared descriptively.

For investigator assessed- ORR (primary efficacy variable), number and percentage of responders will be displayed per treatment arm along with its 95% confidence interval according to Clopper-Pearson.

Statistical inference will be based on the thresholds defined by the Simon's 2-stage design. At the final analysis, the null hypothesis of an ORR of ≤5% will be rejected if >3 patients out of a total of 29 patients respond (CR/iCR/PR/iPR). In the case of dropouts, appropriate statistical methods will be applied to correct for the deviation from the planned sample size.

Number and percentage of patients per RECIST tumor response category will be displayed for each scheduled tumor assessment time point.

Safety: All safety analyses will be performed on the safety analysis set.

Number of TEAEs, SAEs, and adverse events of special interest (AESIs) with a MedDRA System Organ Class and Preferred Term will be assessed. Number and percentage of patients with a TEAE, SAE, or AESI for IFX-1 (Arm A) and for IFX-1 and pembrolizumab (Arm B) will be assessed.

Where adverse events (AEs) are grouped by NCI CTCAE grade or relationship, the maximum grade/relationship per patient and class of AE will be considered. Analyses will be performed for the treatment period and the follow-up period separately.

Safety laboratory, vital signs, and 12-lead electrocardiogram parameters will be analyzed by summary statistics for absolute values and changes from baseline by visit. Shift tables comparing baseline and the worst post-baseline assessment will be prepared if applicable.

Categorical safety parameters will be summarized by absolute and relative frequencies by time point.

Pharmacokinetics and pharmacodynamics: Actual PK sampling times will be determined, and IFX-1 plasma concentration assessed by time point. Summary statistics will be provided for the PK concentrations of IFX-1 at all measured time points including the geometric mean and its coefficient of variation. PK and pharmacodynamics parameters will be analyzed descriptively.

2. SCHEDULE OF ASSESSMENTS

Table 1 Schedule of Assessments

Treatment Cycle 1: 7 weeks/49 days All following cycles: 6 weeks/42 days	Screening Period[1]	Treatment Period (Cycle = C, Day of respective Cycle = D)								Follow-Up (FU) Period		
		Cycle 1						From Cycle 2 on		EOT Visit[2]	Every 12 weeks from EOT Visit (±7d)	EOS (= last FU)
		Day 1		Day 4 (±1d)	Day 8 (±1d)	Day 15 (±1d)	Days 22 (±1d) 36 (±1d)	Day 1 (±3d)	Days 15, 29 (±3d)			
		Pre-Dose	Post-Dose									
Informed Consent	X											
Inclusion/exclusion criteria	X	X										
(Archival) Biopsy for confirmation of locally advanced cSCC diagnosis[3]	X											
Demography, medical and disease history (incl. hepatitis), prior medication	X											
Disease/response assessments[4] (chest, abdomen, pelvis)	X							X		X	Only if discontinuation of IFX-1 treatment for other reasons than PD/iCPD	
Quality of Life assessment	X	X						X		X	X	X
Concomitant disease	X	X		X	X	X	X	X	X	X		
Concomitant medication	X	X		X	X	X	X	X	X	X		
Re-dosing criteria				X	X	X	X	X	X			
IMP administration IV												
IFX-1[5]		X		X	X	X	X	X	X			
Pembrolizumab[6]					X			X				
Safety assessments												
Weight	X	X		X	X	X	X	X	X	X		
Height	X											
Physical examination/ ECOG PS	X	X		X	X	X	X	X	X	X		
Vital signs[7]	X	X	X	X	X	X	X	X	X	X		
Adverse events[8]	X	X	X	X	X	X	X	X	X	X	X	X
Survival status											X	X
12-lead ECG[9]	X	X	X					C2 only		X		
Further antineoplastic therapies											X	X

Treatment Cycle 1: 7 weeks/49 days **All following cycles: 6 weeks/42 days**	**Screening Period[1]**	**Treatment Period** (Cycle = C, Day of respective Cycle = D)							**Follow-Up (FU) Period**		
		Cycle 1					**From Cycle 2 on**		**EOT Visit[2]**	**Every 12 weeks from EOT Visit** (±7d)	**EOS (= last FU)**
		Day 1		**Day 4** (±1d)	**Day 8** (±1d)	**Day 15** (±1d)	**Days 22** (±1d) **36** (±1d)	**Day 1** (±3d)	**Days 15, 29** (±3d)			
		Pre-Dose	Post-Dose									
Safety laboratory (± 3 days)												
Hematology[10]	X	X			X	X	X	X	C2 only	X		
Biochemistry[11]	X	X			X	X	X	X	C2 only	X		
Coagulation parameters[12]	X	X						C2 only		X		
Urine analysis[13]	X	X			X	X	X	X	C2 only	X		
TSH, total T3, free T4[14]	X				X			X		X		
Pregnancy test (WOCBP)[15]	X				X		X	X	X	X	First FU	
PK/immunogenicity/Biomarker assessment												
Complement:[16] C3a (C1D1 only) C5a		X			X	X	X	C2,3, 5, then every other cycle		X	First FU	
ADAs for IFX-1 (mandatory)[17]		X				X	X	C2, 3, 5, then every other cycle		X	First FU	
Pharmacokinetics (mandatory)[18]		X	X		X	X	D22 pre- & post-dose D36 pre-dose only	C2, 3, 5, then every other cycle		X	First FU	
Skin cancer biopsy (or metastasis biopsy)[19] Mandatory	X							Only Stage 2 patients				
Optional								Only Stage 2 patients only at CR/iCR/PR/iPR and/or PD				

(1) Screening: ≤4 weeks prior to the first administration of IFX-1.
(2) End of treatment (EOT) Visit to be performed 30 days after the last IFX-1 or pembrolizumab administration or before the patient starts on another antineoplastic therapy, whichever occurs earlier.
(3) Locally advanced cSCC patient to provide archived or newly obtained tumor material for central pathology review for confirmation of diagnosis of cSCC.
(4) Disease/Response assessment according to modified response evaluation criteria in solid tumors (RECIST) version 1.1/RECIST for immune related therapeutics (iRECIST) (magnetic resonance imaging, computed tomography (CT), or CT scan with contrast, of chest, abdomen, pelvis (and other regions where metastases are suspected). Standardized medical photography of ≥1 index skin tumor must be added. Re-assessments must be made with the same imaging technique as used at baseline. Imaging will also be performed at time of complete response (CR) confirmation. Response assessments to be performed ±7 days. In case patients experience a partial response (PR)/confirmed PR (iPR) or CR/confirmed CR (iCR) that lasts ≥1 year, imaging frequency can be decreased to every other cycle.
(5) IFX-1 administration by intravenous route as 30-minute (-5/+10 minutes) infusion, followed by at least 60 minutes of observation. Start of administration should be seen as “H0”.
(6) Pembrolizumab administration ends 60 minutes (±10 minutes) before IFX-1 infusion start. Pembrolizumab by intravenous route as 30-minute (-5/+10 minutes) infusion, followed by at least 60 minutes of observation.
(7) Vital signs: heart rate, blood pressure (diastolic and systolic), body temperature, and respiratory rate to be performed at each visit, at pre-dose, and H0+1h (±5 minutes) on the days of administration and whenever medically indicated
(8) FU every 3 months until 12 months after EOT Visit. All adverse events (AEs) with onset during treatment until EOT Visit will have to be followed until the outcome of the event is “recovering” (for chronic conditions) or until the end of study (EOS = last FU), and until all queries related to these AEs have been resolved. New related serious adverse events (SAEs) with onset during the follow up period (from the EOT Visit until the EOS) will have to be collected. FU visits may occur by telephone contact, if applicable.
(9) 12-lead electrocardiogram (ECG): at screening, on C1D1 pre-dose and at H0+1 (±5 minutes), on C2D1 at H0+1 (±5 minutes), and at the EOT Visit
(10) Hematology: red blood cells (RBC), white blood cells (WBC) with differential count, platelet count, hemoglobin, mean corpuscular volume (MCV) and hematocrit
(11) Biochemistry: sodium, potassium, calcium, magnesium, alkaline phosphatase (ALP), total bilirubin, lactate dehydrogenase (LDH), aspartate aminotransferase (serum glutamic oxaloacetic transaminase (AST [SGOT]), alanine aminotransferase (serum glutamic pyruvic transaminase) (ALT [SGPT]), glucose, total proteins, albumin, urea, uric acid, creatinine, and C reactive protein (CRP).
(12) Coagulation: activated partial thromboplastin time (aPTT), prothrombin time (PT).
(13) Urine analysis: PH, glucose, leucocytes, proteins, blood.
(14) Preferably Total T3, Free T4 should be analyzed, or other T3/T4 fractions (depending on local standards).
(15) Pregnancy testing (WOCBP: women of childbearing potential only): During screening: serum beta-human chorionic gonadotropin test within 72 hours before first drug administration. During treatment period: urine pregnancy test. During FU urine pregnancy test on the first FU visit for Arm A, on the first FU visit and 120 days after the last dose of pembrolizumab for Arm B
(16) Complement: C5a to be performed at pre-dose during treatment period.C3a to be performed only at C1D1 [pre-dose]
(17) Antidrug antibodies (ADAs) against IFX-1 to be performed at pre-dose during treatment period.
(18) Pharmacokinetics: To be performed at pre-dose during treatment period and in addition at the end of infusion H0+0.5h (-5/+10 minutes, but not before the end of IFX-1 administration) on Cycle 1 Days 1 and 22.
(19) Punch biopsies (skin lesion, whenever possible) and biopsy of a metastasis (only if punch biopsy of a skin lesion is not possible) are to be obtained at screening (all patients) and at C2D1 (+/- 2 days; only patients in Stage 2). Sampling must be obtained at minimal clinical risk from an area that has not been previously irradiated. Additional optional biopsies should be obtained from patients enrolled in Stage 2 at the time of CR/iCR/PR/iPR and/or Progressive Disease is diagnosed.

3. INTRODUCTION AND BACKGROUND INFORMATION

3.1. Background

Non-melanoma skin cancer (NMSC) is the most frequent malignant neoplasm in white populations, with dramatically increasing incidence rates over the last decades (Eigentler et al., 2017).

A systematic analysis for the global burden of disease study revealed 7.7 million (95% uncertainty interval, 5.3-10.6 million) incident cancer cases of NMSC worldwide with 65,000 cancer deaths in 2017. Among cases of NMSC, 1.8 million were identified worldwide cases of squamous cell carcinoma (SCC; Fitzmaurice et al., 2019).

Cutaneous SCC (cSCC) is a common skin cancer characterized by the malignant proliferation of keratinizing cells of the epidermis or its appendages. cSCC usually arises from precursor lesions such as actinic keratosis, and Bowen's disease (SCC in situ) but can also grow de novo or on irradiated skin with or without manifestations of chronic radio dermatitis, or on chronically inflamed skin such as in chronic wounds or chronic inflammatory skin disorders (Stratigos et al., 2015).

The pathogenesis of cSCC is multifactorial and includes many extrinsic and intrinsic factors. The most important extrinsic factor is generally recognized to be ultraviolet (UV) sunlight exposure. As lifetime UV exposure increases, so does the incidence of cSCC. Other extrinsic factors that are related to the development of cSCC are industrial carcinogens, such as pitch, tar, or fuel oil (Shulstad and Proper 2010). Some targeted anticancer therapies, such as inhibitors of B-raf protein, can promote eruptive cSCC via other mechanisms, i.e., by boosting the effect of pre-existing mutations in chronically sun-exposed areas (Boussemart et al., 2013). Intrinsic factors associated with cSCC include age, lighter skin pigmentation, scars, dermatoses associated with photosensitivity (chronic cutaneous lupus), ulcerations, and lichen planus (Shulstad and Proper 2010). cSCC is rare under the age of 45, its incidence dramatically increasing with age (Stratigos et al., 2015). It is also very prevalent in patients who are immunosuppressed and these patients experience higher recurrence rates and decreased survival (Manyam et al., 2017).

In contrast to basal cell carcinoma, which very rarely metastasizes, cSCC has the potential to metastasize initially to regional lymph nodes and subsequently to distant sites. The rate of metastasis in cSCC has been estimated to range from 2% to 5%. While its distant metastatic potential is comparatively low, the presence of distant metastasis is associated with a dismal prognosis and a median survival of less than 2 years. Thus, it is crucial to preserve the general high chances of cure of cSCCs by a careful evaluation and proper early management of all cases. The potential aggressiveness of this tumor should not be underestimated (Stratigos et al., 2015).

Clinical Presentation and Prognosis

The most common clinical appearance of invasive cSCC is an actinic keratosis that becomes hyperkeratotic or its base becomes infiltrated, or else becomes tender or ulcerated (Stratigos et al., 2015). While most cSCCs will arise in the context of actinic keratosis, the rate of transformation of actinic keratosis into invasive cSCC is apparently low, at least in a few years period of follow-up (<1/1000 cases per year during a 5-year follow-up) (Marks et al., 1988; Werner et al., 2013). Notably, the progression appears to be more frequent in actinic keratosis harboring persistent beta papilloma virus infections (Stratigos et al., 2015).

When the tumor arises de novo or the early keratosis phase is lacking, cSCC can present as an asymptomatic small plaque or nodule that enlarges over time. It can become crateriform ('keratoacanthoma-like'), ulcerated, necrotic, or botryomycotic. Alternatively, patients may present with a flat ulcer with a raised border (Stratigos et al., 2015).

The potential for local recurrence or metastasis of cSCC varies with the pathologic variant, localization of the primary lesion, perineural invasiveness, and differentiation grade (verrucous, spindle, desmoplastic, acantholytic, or adenosquamous) (National Comprehensive Cancer Network [NCCN] Guideline on Squamous Cell Skin Cancer version 1.0, 2020; Stratigos et al., 2015).

Overall, advanced SCC has a dismal prognosis and 10-year survival rates are less than 20% for patients with regional lymph node involvement and less than 10% for patients with distant metastases (Hillen et al., 2018). Patients with distant metastases have median survival of less than 2 years (Stratigos et al., 2015).

Treatment of the Disease

The goals of primary treatment of cSCC are the cure of the tumor and the preservation of function and cosmesis.

The primary treatment for cSCC is usually surgical excision with predetermined margins; however, other locally destructive techniques (e.g., cryotherapy or electrodessication and curettage, non-surgical treatments including topical imiquimod, and photodynamic therapy) can be employed as indicated, especially for smaller lesions (Stratigos et al., 2015; NCCN 2020).

A small percentage of cSCC cases is recalcitrant to surgical therapies and may display aggressive biology with local recurrences and/or lymphatic spread (Hanlon, 2013). In clinics, of the total of patients requiring systemic therapy, approximately 50% have locally advanced and 50% metastasized cSCC (Hillen et al., 2018).

In the presence of clinically detectable nodal disease, regional lymph node dissection is recommended (Stratigos et al., 2015). Guidelines also recommend that adjuvant or post-operative radiotherapy can be considered where there is substantial perineural involvement, when tissue margins are not tumor-free after surgical excision, and in the presence of regional disease (NCCN 2020; SIGN, 2014; Stratigos et al., 2015). The NCCN guideline suggests that adding radiotherapy to lymph node dissection improves disease-free survival (NCCN 2020). Evidence on the use of systemic chemotherapy, either alone or in combination with radiotherapy, in the management of cSCC comes mainly from small case series (SIGN, 2014). Agents that have been used include cisplatin, or carboplatin, 5-fluorouracil, bleomycin, methotrexate, adriamycin, taxanes, gemcitabine, ifosfomide, vindesine, mitomycin C, interferon, or doxorubicin (SIGN, 2014; Stratigos et al., 2015). However, responses are mostly short lived and do not lead to a curative effect (Stratigos et al., 2015). The NCCN guideline mentions cisplatin (either alone or in combination with 5-fluorouracil) or carboplatin as chemotherapeutic options for some patients with inoperable or incompletely resected regional disease, although data supporting their efficacy for this indication are limited (NCCN 2020).

In 2018, the antiprogrammed cell death 1 protein (PD-1) antibody cemiplimab was the first drug that has been approved for the treatment of locally advanced and metastatic cSCC in the United States. Approval was granted based on single arm, Phase II studies showing an unprecedented 50% overall best response in both disease stages (Migden et al., 2018). In the European Union, cemiplimab was authorized in June 2019 for the treatment of adult patients with metastatic or locally advanced cSCC who are not candidates for curative surgery or curative radiation. However, patients who do not respond to cemiplimab have no effective treatment options and a dismal prognosis with a median overall survival (OS) of <1 year.

The importance of anti-PD-1 antibodies has been further supported by data on treatment with the PD-1 inhibitor pembrolizumab. A Phase II study with pembrolizumab on 39 patients with unresectable cSCC, with no prior systemic treatment and a median age of 80 years, showed a response rate of 42% and a median progression-free survival (PFS) of around 7 months (reviewed in Ascierto and Schadendorf, 2019).

On June 24, 2020, the Food and Drug Administration of the USA approved pembrolizumab (KEYTRUDA, Merck & Co., Inc.) for patients with recurrent or metastatic cutaneous squamous cell carcinoma (cSCC) that is not curable by surgery or radiation.

For patients who have progressed on PD-1 therapies no satisfactory, efficacious treatment is available.

3.2. Study Rationale

3.2.1. Drug Profiles

3.2.1.1. IFX-1

IFX-1 is a novel immunoglobulin G4 (IgG4) monoclonal antihuman C5a -antibody, which specifically binds to the soluble human complement split product C5a. IFX-1 has been demonstrated to block C5a-mediated biological effects with high efficacy in vitro. C5a is one of the most potent inflammatory factors, triggering innate immune responses and bridging to adaptive immune responses (Dunkelberger and Song, 2010). In blood, C5 is cleaved to C5a by components of the classical and alternative complement pathway, and the coagulation pathway, whereas in tissue, factors of the alternative complement and the coagulation pathway factors play a major role in C5a generation (Hess and Kemper, 2016).

3.2.1.2. Pembrolizumab

Pembrolizumab is a potent humanized IgG4 monoclonal antibody (mAb) with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications and detailed background information refer to the Investigator's Brochure (IB).

3.2.2. Non-clinical and Therapeutic Studies

3.2.2.1. IFX-1

Non-clinical studies were conducted to assess pharmacological and toxicological aspects of IFX-1 and showed that IFX-1 was able to rapidly bind to its target, the human C5a, and achieve an almost complete blockade of C5a-induced biological effects. At the same time, cleavage of C5 and formation of the complement membrane attack complex was not disrupted in vitro.

IFX-1 did not demonstrate any cross-reactivity or bioactivity in species other than humans and non-human primates (Section 4.2 of the IB). Therefore, toxicology studies were only conducted in cynomolgus monkeys. None of the Good Laboratory Practice-compliant studies in cynomolgus monkeys revealed relevant toxicological or safety concerns for IFX-1. During single-dose and repeat-dose administration of IFX-1 at doses of up to [redacted] mg/kg body weight in cynomolgus monkeys no direct IFX-1-related toxicological or adverse findings within an extended core battery of safety pharmacology assessments were observed. Results showed dose-related increases in systemic and maximum exposure in the investigated dose range of [redacted] mg/kg body weight. Antidrug antibodies (ADAs) were detected in [redacted] animal in the 26-week repeat-dose study. [redacted] died, most likely because of an ADA-mediated immune complex formation.

An overview of the non-clinical toxicology studies that were conducted with IFX-1 is available in Table 8 of the IB.

For further details refer to Section 4 of the IB.

3.2.2.2. Pembrolizumab

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of -tumor-specific CD8+ T cells and ultimately leads to tumor rejection, either as a monotherapy or in combination with other treatment modalities (Hirano et al., 2005; Blank et al., 2004; Weber, 2010; Strome et al., 2003; Spranger et al., 2014; Curran et al., 2010; Pilon-Thomas et al., 2010). Anti-mouse PD-1 or antimouse PD-L1 antibodies have demonstrated anti-tumor responses in models of SCC, pancreatic carcinoma, melanoma, acute myeloid leukemia, and colorectal carcinoma (Strome et al., 2003; Curran et al., 2010; Pilon-Thomas et al., 2010; Nomi et al., 2007; Zhang et al., 2004). In such studies, tumor infiltration by CD8+ T cells and increased interferon gamma, granzyme B, and perforin expression were observed, indicating that the mechanism underlying the antitumor activity of PD-1 checkpoint inhibition involved local infiltration and activation of effector T cell function in vivo (Curran et al., 2010). Experiments have confirmed the in vivo efficacy of anti-mouse PD-1 antibody as a monotherapy, as well as in combination with chemotherapy, in syngeneic mouse tumor models.

For further details refer to the IB.

3.2.3. Experience in Humans

3.2.3.1. IFX-1

IFX-1 is being developed for the treatment of inflammatory diseases. Five clinical studies in humans have been completed so far. One Phase I study in healthy volunteers (Study IFX-1-P1.1) and four Phase II studies; one study in patients with early septic organ dysfunction (Study IFX-1-P2.1), one study in patients undergoing complex cardiac surgery (Study IFX-1-P2.2), and two studies in patients with hidradenitis suppurativa (HS; Study IFX-1-P2.3 and Study IFX-1-P2.4).

As of 01 November 2019, IFX-1 safety had been assessed in approximately [redacted] subjects. IFX-1 was safe and well tolerated, with no dose relationship in the safety findings. No specific adverse reactions emerged in clinical studies of single or multiple doses IFX-1 in healthy volunteers or patients with cardiac disease, sepsis, or HS.

Currently, four further Phase II studies are ongoing; two studies in patients with granulomatosis with polyangiitis and microscopic polyangiitis (also referred to as antineutrophil cytoplasmic antibody-associated vasculitis; Study IFX-1-P2.5 and IFX-1-P2.6), one study in patients with pyoderma gangrenous (Study IFX-1-P2.7) and one study in severe COVID-19 pneumonia (Study IFX-1-P2.9).

Treatment with IFX-1 was safe and well tolerated with rare occurrence of adverse events (AEs) of special interest (AESIs) that were defined as [redacted]. As of December 11, 2019, [redacted] patients experienced AEs suggestive of [redacted]. The reactions were moderate, and treatment continued with adequate prophylactic medication. ADAs during treatment were observed in a range of [redacted]% with a trend towards increasing frequency with low dose and larger administration intervals.

3.2.3.2. Pembrolizumab

Extensive clinical experience is available for pembrolizumab, either as single agent therapy or in combination with mAbs, chemotherapies, and radiotherapy. This has been reported by several authors and is regularly updated by the US Food and Drug Administration and the EU Medicines Agency in the respective prescribing information.

The major on-target side effects of single agent pembrolizumab are infusion-related reactions and immune-related AEs (irAEs; including but not limited to pneumonitis, colitis, hepatitis, and endocrinopathies).

Other common pembrolizumab-related AEs are fatigue, musculoskeletal pain, decreased appetite, pruritus, diarrhea, nausea, rash, pyrexia, cough, dyspnea, constipation, pain, and abdominal pain.

A comparison of several immune checkpoint inhibitor therapies across solid tumors alone or in combination with conventional anticancer therapy showed that PD-1 or PD-L1 checkpoint inhibitors have a favorable safety profile and can be safely combined with other antibodies and small molecules without leading to unforeseen AEs (Xu et al., 2018). An overlap of toxicities was most often seen with immune checkpoint inhibitors targeting cytotoxic T-lymphocyte-associated antigen 4. When combining immune checkpoint inhibitor therapy with chemotherapy or with small therapeutic molecules, drug-specific toxicities are combined rather than potentiated.

3.2.4. Scientific Rationale for the Study

In the context of cancer, C5 can be produced by a plethora of tissue-resident cells, such as immune, stromal, and tumor cells. Tissue-present plasmin, trypsin, thrombin, and coagulation factors can then cleave C5a from C5 (Amara et al., 2010; Corrales et al., 2012). Recent scientific data imply the C5a/C5a receptor (C5aR) axis as a potential driver for tumorigenesis and metastases particularly in the context of SCC (Medler et al., 2018).

C5a has been shown to increase metastatic potential by increasing epithelial-to-mesenchymal transition, tumor cell motility, and vascular permeability and to foster an immunosuppressive tumor microenvironment (TME) (Markiewski et al., 2008; Nitta et al., 2016; Hu et al., 2016). Medler et al., 2018 showed in the TME of SCC in mice that C5a is being split from C5 by plasmin, whereas plasmin is produced by urokinase plasminogen activator (uPA)-positive mast cells. The latter stem from myeloid derived cells, which express C5aR and are attracted by C5a to the TME.

In addition, C5a drives macrophages from a M1- to an immunosuppressive M2-like type and limits CD8 T cell activity (Markiewski et al., 2008). Consequently, tumor development was decreased in a similar extent in either C5a receptor (C5aR)-deficient or in uPA-deficient mice (Medler et al., 2018). Of note, C5aR, uPA, and uPA receptor overexpression is described for human SCC, including cSCC, and has been linked to decreased survival (Imamura et al., 2016; Nitta et al., 2016; Chen et al., 2018; Wada et al., 2016; Rømer et al., 2001; Christensen et al., 2017).

Moreover, C5a can induce PD-L1 on human monocytes (An et al., 2016). PD-L1 is overexpressed by human cSCC and other forms of SCC including non-small cell lung cancer (NSCLC). In addition, PD-L1 expressing tumor-associated macrophages have been linked to PD-1 checkpoint inhibitor failure in the treatment of patients with NSCLC (Liu et al., 2019).

Along that line, in a PD-1 inhibitor resistant melanoma mouse model, the combination of a C5a/C5aR pathway inhibitor with inhibition of the PD-1/PD-L1 axis showed a strong antitumoral effect, which was weaker when one of the axes was inhibited alone (Ajona et al., 2017; Zha et al., 2017).

Based on these findings, it is planned to investigate the antitumoral activity of the clinical stage C5a-inhibitor IFX-1 alone or in combination with a PD-1 inhibitory antibody in PD-1/PD-L1-resistant or refractory cSCC.

3.2.5. Justification for Dose

3.2.5.1. IFX-1

The aim when determining the dose and administration frequency for IFX-1 is to achieve complete or nearly complete inhibition of C5a signaling at the C5a receptors at the tumor site. In addition, it was regarded as important to establish a convenient administration schedule for the elderly patient population being treated for locally advanced and metastatic cSCC. IFX-1 dose and administration schedule were chosen based on pharmacokinetic (PK) and pharmacodynamic observations and modeling based on human data obtained in the studies conducted to date.

The observed half-life of IFX-1 with a single dose of 800 mg was 3 to 4 days in Study IFX-1-P2.2 in patients undergoing complex cardiac surgery. Thus, an additional dose of 800 mg at Day 4, followed by weekly (QW) administration of 800 mg IFX-1 has been chosen for Study IFX-1-P2.3 in patients with HS. This fractionated loading dose, 800 mg administered on days 1, 4, and 8 was well tolerated.

In Study IFX-1-P2.3 in patients with HS, 800 mg QW IFX-1 was administered for up to 9 times including the additional dose of 800 mg at Day 4. This administration schedule resulted in IFX-1 trough concentrations of around [redacted] µg/mL and a decrease of elevated baseline C5a levels to approximately detection limit throughout the treatment duration in the majority of patients. This dosing regimen, providing the same overall drug exposure for the duration of the study (fractionated loading dose of 800 mg IFX-1 each on days 1, 4, 8, followed by weekly exposure to

800 mg) as planned in this study, was well tolerated, with no new safety signals, and clinical improvement of HS was observed in some patients.

In another clinical study in HS (Study IFX-1-P2.4), four different dosing schedules have been explored, of which the highest dose of 1200 mg Q2W achieved sufficient IFX-1 levels to decrease elevated baseline plasma C5a levels to approximately normal throughout the administration period of 16 weeks in the majority of patients. Safety findings were similar in all dose groups, and similar to safety findings in previous studies, with no new specific AESIs.

As of July 06, 2020, in the clinical study IFX-1-P2.7 nine doses of 1600 mg Q2W were administered and well tolerated. By the time this study, IFX-1-P2.8, is initiated, dose escalation in study IFX-1-P2.7 will have progressed to higher doses of 2400 mg unless a DLT will have been experienced.

Based on the available data of studies IFX-1-P2.3 and IFX-1-P2.4, a PK model has been developed in order to understand the PK of IFX-1. ("Abbreviated Population Pharmacokinetic/ Pharmacodynamic Modeling Report for IFX-1", 06 April 2020). The population PK model described the PK as [redacted] clearance with elimination at clinical concentrations being [redacted]. This means that this PK model is transferable between indications even when concentrations of C5a are different. The target-dependent Michaelis-Menten component of the clearance is [redacted] at most clinical concentrations, as the Km is estimated to be [redacted] ng/ml. This translates into a target C_{min} of [redacted] ng/ml in order to fully saturate the target C5a and therefore to minimize its signaling to its receptors. This PK result is also supported by the fact that a C_{trough} threshold of [redacted] ng/ml for IFX-1 [redacted] µg/ml) was found to be correlated with clinical response. The 1600 mg Q2W dose was the lowest dose that on average could keep the IFX-1 concentrations for greater than [redacted] of the dosing period above the threshold of [redacted] ng/ml. Simulations of the dosing regimens indicates that when dosing patients with 1200 mg Q2W, [redacted] % of the patients will achieve a trough concentration [redacted] ng/ml, while when dosing patients with 1600 mg Q2W, [redacted] of the patients will remain above the threshold of [redacted] ng/ml throughout the entire dosing interval. Moreover, at the dose of 1600 mg Q2W [redacted] of 1000 simulated patients crossed the NOAELs of [redacted] mcg/ml and [redacted] mcg/ml defined by the toxicology studies.

A sophisticated physiology-based PK modelling report was created based on existing data specifically for the indication cSCC ("IFX-1 PBPK Modelling For Cutaneous Squamous Cell Carcinoma (non-melanoma skin cancer)", September 2019). This analysis similarly indicates that at doses [redacted] mg/kg the linear clearance [redacted] over the target-mediated catabolism. Regarding blockage of C5a binding to C5aR, this was found to be incomplete for the HS patients in study IFX-1-P2.3 receiving [redacted], indicating that increasing the dose may be beneficial. The modelling report states that for cSCC patients receiving the dose of [redacted], the blockage of the C5a-C5aR interaction in tumor is considered sufficient with [redacted] % inhibition throughout the whole therapeutic treatment. However, this is contingent on a number of assumptions, which cannot be confirmed by experimental means. Taking into account this

uncertainty and the high variability of the pharmacokinetic data, a higher dose than [redacted] is considered to increase the likelihood that treated cSCC patient will receive a dose that is sufficient to provide optimal therapeutic effects.

Based on these results, the dose of 1600 mg Q2W is considered to be the target dose for this Phase II study and, if supported by the results, for future confirmatory studies.

3.2.5.2. Pembrolizumab

The planned dose of pembrolizumab for this study is 400 mg every 6 weeks (Q6W). A 400 mg Q6W dosing regimen of pembrolizumab is expected to have a similar benefit-risk profile as 200 mg every 3 weeks (Q3W), in all treatment settings in which 200 mg Q3W pembrolizumab is currently approved (see pembrolizumab IB for details). Specifically, the dosing regimen of 400 mg Q6W for pembrolizumab is considered adequate based on modeling and simulation analyses, given the following rationale:

- PK simulations demonstrating that in terms of pembrolizumab exposures:
  - Average concentration over the dosing interval (C_{avg}) (or area under the curve [AUC]) at 400 mg Q6W is similar to that at the approved 200 mg Q3W dose, thus bridging efficacy between dosing regimens.
  - Trough concentrations (C_{trough}) at 400 mg Q6W are generally within the range of those achieved with 2 mg/kg or 200 mg Q3W in the majority (>99%) of patients.
  - Peak concentrations (C_{max}) at 400 mg Q6W are well below the C_{max} for the highest clinically tested dose of 10 mg/kg Q2W, supporting that the safety profile for 400 mg Q6W should be comparable to the established safety profile of pembrolizumab.
- Exposure-response for pembrolizumab has been demonstrated to be flat across indications, and OS predictions in melanoma and NSCLC demonstrate that efficacy at 400 mg Q6W is expected to be similar to that at 200 mg or 2 mg/kg Q3W, given the similar exposures, thus 400 mg Q6W is expected to be efficacious across indications.

On June 24, 2020, the Food and Drug Administration of the USA approved pembrolizumab (KEYTRUDA, Merck & Co., Inc.) for patients with recurrent or metastatic cutaneous squamous cell carcinoma (cSCC) that is not curable by surgery or radiation. The recommended pembrolizumab doses for cSCC are 200 mg every 3 weeks or 400 mg every 6 weeks.

3.3. Benefit/Risk Assessment

IFX-1 is a drug that has been safely administered to more than 300 subjects. In non-clinical safety studies, a NOAEL of [redacted] mg/kg has been established resulting in pharmacokinetic NOAEL PK values, which will not be reached in this study based on the simulations stated in section 3.2.5.1 of this protocol. [redacted] unexplained death occurred in [redacted] cynomolgus monkey during the non-clinical safety studies, which retrospectively showed development of anti-IFX-1 antibodies, and resulting circulating immune complexes, which has been described in monkeys before. In humans, this chimeric IgG4 antibody has the potential to elicit infusion-related reactions, including

hypersensitivity or anaphylaxis. However, there have only been few cases of anti-IFX-1 antibody formation, and only mild to moderate signs of hypersensitivity reactions were observed so far in study patients (overall ADA rate in the range of [redacted]%). In total, IFX-1 showed very good tolerability in clinical studies. The majority of observed AEs were attributed to the underlying diseases and IFX-1 AESIs occurred occasionally (see IFX-1 IB for details).

Preclinically, C5a has been shown to support tumor development and metastasis and to contribute to an immunosuppressive TME, in particular in SCC. In addition, the combination of anti-C5a and anti-PD1 directed therapy led to tumor regressions in antiPD1 therapy resistant melanoma mouse models.

IFX-1 leads to an almost complete blockade of C5a-induced biological effects and prevents C5a-mediated inflammatory signaling. In vitro and in vivo, C5a blockade does not interfere with activation of the classical component cascade, generation of other anaphylatoxins C3a and C4a, and assembling of the membrane attack complex.

The potential risks associated with the intravenous administration of IFX-1 due to its mode of action include the following:

Infections: Potent inflammatory response mechanisms, such as neutrophil oxygen radical species generation, are decreased upon C5a blockade. Infections are therefore identified as an anticipated important potential risk associated with IFX-1 treatment (Section 7.6.4 of the IFX-1 IB). Therefore, investigators (and other health care professionals) should be vigilant for signs and symptoms of infections in general. [redacted]

Meningitis/meningococcal sepsis: To date, no cases of meningitis or meningococcal sepsis have been reported in clinical studies with IFX-1 (Section 7.6.3 of the IFX-1 IB). Therefore, mandatory vaccination or concomitant broad-spectrum antibiotic treatment is not warranted based on the mode of action for IFX-1. However, until more patients have been exposed to IFX-1, specific attention should be given to any signs of meningitis in this context and immediate appropriate measures should be taken as described in Section 7.6.3 of the IFX-1 IB. [redacted]

Infusion-related reactions/hypersensitivity reactions: Because IFX-1 is an antibody/protein, a general risk for infusion-related reactions, including hypersensitivity or anaphylaxis, exists (Section 7.6.2 of the IFX-1 IB). Participating study sites are required to be able to provide adequate treatment and care in case of an anaphylactic reaction. To date, no anaphylactic reactions have been reported after administration of IFX-1 in completed clinical Phase I and Phase II studies. [redacted]

So far, the PD-1 checkpoint inhibitors cemiplimab and pembrolizumab are the only approved therapies for locally advanced or metastatic cSCC. For patients with locally advanced or metastatic

cSCC, who have not responded or have progressed on cemiplimab, pembrolizumab, or another PD-1/PD-L1-directed therapy, no other efficacious therapy exists currently.

Because no efficacious therapy is currently available in the setting of PD-1 or PD-L1-refractory or resistant locally advanced or metastatic cSCC and a good AE profile was observed for IFX-1 so far, the hypothesized benefit outweighs the potential risks for the patients participating in this study.

More detailed information about IFX-1, the known and expected benefits and risks, including safety experience gained in clinical studies investigating inflammatory diseases, may be found in the IB.

4. OBJECTIVES AND ENDPOINTS

4.1. Study Objectives

4.1.1. Monotherapy Arm A

Primary objective:

- To assess the antitumor activity of IFX-1

Secondary objectives:

- To further assess efficacy of IFX-1
- To assess the safety profile of IFX-1
- To assess the PK of IFX-1
- To monitor the immunogenicity of IFX-1
- To assess the impact of IFX-1 on quality of life (QoL)

Other objectives:

- To describe the TME in primary tumor samples and metastases
- To assess pharmacodynamic effects of IFX-1 in skin tumors and peripheral blood
- To describe oncogenic alterations of the tumor at baseline

4.1.2. Combination Therapy Arm B

Primary objectives:

Safety run-in part

- To determine the maximum tolerated dose (MTD) or recommended Phase II dose (RP2D)

Phase II portion

- To assess the antitumor activity of IFX-1 + pembrolizumab
- To assess the safety profile of IFX-1 + pembrolizumab

Secondary objectives:

- To further assess efficacy of IFX-1
- To assess the PK of IFX-1
- To monitor the immunogenicity of IFX-1
- To assess the impact of IFX-1 + pembrolizumab on QoL

Other objectives:

- To describe the TME in primary tumor samples and metastases
- To assess the pharmacodynamic effects of IFX-1 + pembrolizumab in skin tumors and peripheral blood
- To describe oncogenic alterations of the tumor at baseline

4.2. Study Endpoints

4.2.1. Primary Endpoints

4.2.1.1. Monotherapy Arm A

The primary endpoint of monotherapy Arm A is investigator assessed best overall response rate (ORR) for IFX-1, with response being defined as best response of complete response (CR)/confirmed CR (iCR) or partial response (PR)/confirmed PR (iPR) per modified response evaluation criteria in solid tumors (RECIST) version 1.1/RECIST for immune-related therapeutics (iRECIST).

4.2.1.2. Combination Therapy Arm B

Safety run-in part

The primary endpoint of the safety run-in part of combination therapy Arm B is the frequency of dose-limiting toxicities (DLTs) by dose cohort.

Phase II portion

The co-primary endpoints of the Phase II portion of Arm B are investigator assessed best ORR for IFX-1 + pembrolizumab, with response being defined as best response of CR/confirmed CR (iCR) or PR/confirmed PR (iPR) per modified RECIST v1.1/iRECIST and frequency, severity, and investigational new drug (IND) attribution of TEAE and serious adverse event (SAE) according

to the Medical Dictionary for Regulatory Activities (MedDRA) coding (version valid at time of reporting) and the NCI CTCAE grading system v5.0.

4.2.2. Secondary Endpoints

4.2.2.1. Monotherapy Arm A

Secondary endpoints comprise the following:

- Response (CR/iCR/PR/iPR) and stable disease (SD) duration
- Disease control rate (CR/iCR+PR/iPR+SD)
- PFS
- OS
- Frequency, severity, and IND attribution of treatment-emergent AEs (TEAEs) and SAEs according to MedDRA coding (version valid at time of reporting) and the National Cancer Institute common terminology criteria for AEs (NCI CTCAE) grading system (version 5.0, 27 November 2017)
- Post infusion (C_{max}) and trough concentration (C_{trough}) of IFX-1
- Development of human ADAs against IFX-1
- Changes in QoL as per the European Organisation for Research and Treatment of Cancer (EORTC)-QoL questionnaire (QLQ)-C30 total score

4.2.2.2. Combination Therapy Arm B

Secondary endpoints comprise the following:

- Response (CR/iCR/PR/iPR) and SD duration
- Disease control rate (CR/iCR+PR/iPR+SD)
- PFS
- OS
- C_{max}, and C_{trough} of IFX-1
- Development of human ADAs against IFX-1
- Changes in QoL as per the EORTC-QLQ-C30 total score

4.2.3. Explorative Endpoints

Other endpoints across both arms are:

- Tissue-based biomarkers in skin-based tumor lesions, before and during IFX-1 administration
- C5a concentration in plasma before treatment start, during treatment, and at treatment discontinuation

5. STUDY DESIGN

5.1. Overall Design

The study is an open-label, non-randomized, 2-stage, 2-arm, Phase II study, investigating antitumor activity of IFX-1 alone or IFX-1 in combination with pembrolizumab for the treatment of locally advanced or metastatic PD-1- or PD-L1-resistant/refractory cSCC.

It is planned to include up to approximately 70 patients in the 2 arms: IFX-1 monotherapy Arm A and IFX-1 + pembrolizumab combination therapy Arm B.

Arm A consists of 2 stages where patients will receive IFX-1 monotherapy (see Section 5.2.1).

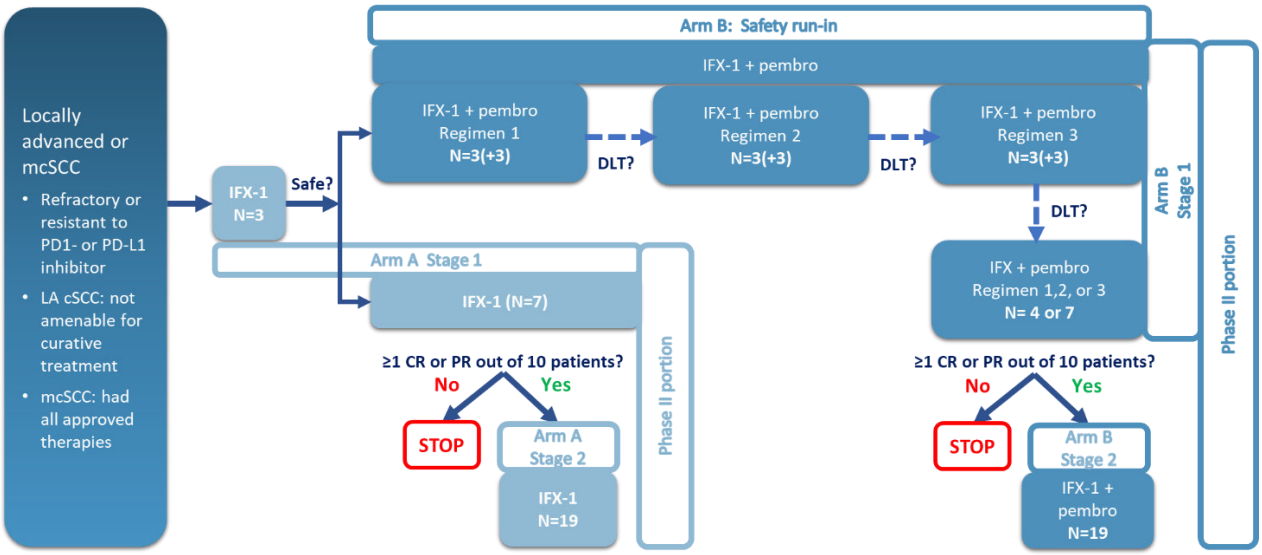
Arm B will start after ≥3 patients have been treated in Arm A and no toxicity concerns have emerged. Arm B consists of a safety run-in part in Stage 1 with 3 dose cohorts, and a Phase II portion in Stage 1 and Stage 2 (see Section 5.2.2 and Figure 1). In the 3 dose cohorts of the safety run-in, escalating doses of IFX-1 will be investigated in combination with 400 mg pembrolizumab every 6 weeks [Q6W], in order to identify the MTD. 6 patients will need to be treated at the MTD or at the highest IFX-1 dose level (Regimen 3, if MTD was not reached) to decide if this dose can be selected as RP2D which will then be explored in the Phase II portion of Arm B. In case only 3 patients will have been previously treated at the MTD or highest IFX-1 dose level, 3 more patients will be added to this cohort. If 6 patients were already treated at the proposed dose level, then additional patients will not be required and the decision on the RP2D will be made based on the available data.

Patients will be treated until disease progression, occurrence of unacceptable toxicity, or treatment discontinuation for any other reason.

Patient enrollment into each of the treatment arms follows an optimal Simon's 2-stage design (Simon, 1989) with an interim analysis of treatment response after Stage 1 prior to patient enrollment into Stage 2 (see Section 10.3.4).

Patients will be assigned to treatment Arm A or B as enrollment rules allow and stratified by locally advanced or metastatic cSCC.

A schematic overview of the overall study design and patient enrollment is given in Figure 1Figure 1 Study Design



CR: complete response; DLT: dose-limiting toxicity; LA: locally advanced; mcSCC: metastatic cutaneous squamous cell carcinoma; N: number of patients; PD1: programmed cell death 1 protein; PD-L1: programmed cell death ligand 1; PR: partial response.

The IFX-1 dosing in Stage 2 of Arm B will be IFX-1 dose in regimens 1, 2, or 3 depending on the maximum tolerated dose (MTD) or recommended Phase II dose (RP2D) from Stage 1. In case only 3 patients have been previously treated at the MTD or highest IFX-1 dose level, then 3 more patients will be enrolled into the respective dose level cohort before the dose can be finally selected for Stage 2.

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A steering committee will be established to support the patient enrollment in both treatment arms and monitor patient safety throughout the study. For further details see Section 5.3.

5.1.1. Method of Treatment Assignment

Patients will be centrally assigned to a treatment arm by the Sponsor according to proceeding of enrollment and safety evaluation by the steering committee (see Section 5.3). Treatment assignment will be stratified by locally advanced or metastatic cSCC; ≥3 out of 10 in Stage 1 and ≥9 out of 29 patients in Stage 2 in each treatment arm must have either locally advanced or metastatic disease at time of (interim) analyses. The investigational medicinal product (IMP) will be centrally assigned using an Interactive Web Response System (IWRS). Before the study is initiated, user access codes (log in information), user instructions, and training will be provided to responsible personnel at each site.

IMP will be dispensed at the study visits as summarized in the schedule of assessments (SoA, Table 1).

Returned IMP must not be re-dispensed to the patients.

5.1.2. Blinding

This is an open-label study; however, the IMP kit numbers will be assigned to each patient using an IWRS. The site will contact the IWRS prior to the start of IMP for each patient. The site will record the IMP assignment on the applicable case report form if required.

5.2. Patient Enrollment

A Simon's 2-stage design will be applied in each independent cohort/treatment arm.

After informed consent, screening procedures are to be performed within 4 weeks before first study treatment administration. For details on the role of the steering committee, see Section 5.3.

5.2.1. Monotherapy Arm A

Three patients will be enrolled in treatment Arm A to receive IFX-1 monotherapy. After these three patients have been treated and their safety closely monitored by the steering committee, as described in Section 5.3, enrollment into Arm A will continue with additional 7 patients. If one or more of the 10 patients enrolled in Stage 1 of Arm A have a response evaluation of PR or CR at their third tumor assessment (no confirmation of response evaluation necessary), enrollment of 19 additional patients in Stage 2 of Arm A will continue without specific enrollment rules. If there are no responders in Stage 1 of Arm A, enrollment will be stopped and there will be no Stage 2 for Arm A.

For the definitions of CR and PR refer to Appendix 3.

5.2.2. Combination Therapy Arm B

5.2.2.1. Safety Run-In

After ≥3 patients have been treated in Arm A under close monitoring by the steering committee, the safety run-in of Stage 1 of treatment Arm B will be opened. Patients will be sequentially enrolled into 3 escalating dose cohorts and their safety will be monitored by the steering committee, as described in Section 5.3.2.

The safety run-in part will follow a 3+3 design as described in 10.3.4.2 and monitored by the steering committee: 3 patients will be enrolled in the lowest dose cohort (IFX-1 regimen 1 + pembrolizumab). If 1 of the 3 patients experiences a DLT (see Section 7.2.2.2.3), the cohort will be expanded to a total of 6 patients. If ≥1 patient of 3 or >1 patient of 6 develop a DLT, further dose escalation is not pursued, and the next lower dose will be chosen as the MTD (see Section 7.2.2.2.4). If there is no DLT observed in any of the first 3 patients, or in only 1 of 6 patients, 3 new patients will be enrolled in the next higher dose cohort (IFX-1 regimen 2 + pembrolizumab). For the second and third dose cohort (IFX-1 regimen 3 + pembrolizumab), the same rules apply. If the MTD is not reached, the highest dose (IFX-1 regimen 3 + pembrolizumab) will be chosen as potential RP2D (see Section 7.2.2.2.4). 6 patients will have to be treated at the highest IFX-1 or MTD dose level to confirm the respective dose to be used in Stage 2. In case only 3 patients will have been previously treated at the MTD or highest IFX-1 dose level, 3 more patients will be added to this cohort. If 6 patients were already treated at the proposed dose level, then additional patients will not be required and the decision on the RP2D will be made based on the available data. When the MTD or RP2D has been established, Stage 1 of Arm B will continue with the Phase II portion (see Section 5.2.2.2).

5.2.2.2. Arm B Phase II Portion

After the MTD or RP2D dose have been identified and confirmed, the safety run-in part is completed and, under close monitoring of the steering committee (see Section 5.3), additional patients will be enrolled in Stage 1 of Arm B until 10 patients will have received the RP2D. If ≥1 of the 10 patients has a response evaluation of PR/iPR or CR/iCR after their third tumor assessment (confirmation not necessary), enrollment of 19 additional patients in Stage 2 of Arm B will continue without specific enrollment rules. If there are no responders in Stage 1 of Arm B, enrollment will be stopped and there will be no Stage 2 for Arm B.

For the definitions of CR/iCR and PR/iPR refer to Appendix 3 and Appendix 4.

5.3. Steering Committee

A steering committee will be constituted to support the patient enrollment in both treatment arms and monitor patient safety throughout the study. The steering committee will include the clinical study monitor and ≥3 cSCC experts (principal investigators included). At all safety reviews performed by the Steering Committee, and when reviewing the overall data prior to progression to

stage 2 of the protocol in each treatment arm, the committee will review the adverse event data in the same way as outlined for the definition of DLTs in Section 7.2.2.2.3. Detailed information will be provided in the Steering Committee Charter.

5.3.1. Monotherapy Arm A

In Arm A, IFX-1 will be dosed as monotherapy utilizing a dosing regimen that is consistent with prior exposures in the HS patient population (study IFX-1-P2.3) and the pyoderma gangrenosum patient population (study IFX-1-P2.7). In Arm A, the Committee will review the safety after three patients have reached day 36 of their treatment. At this point of time, during their treatment they will have received the fractionated loading dose of 800 mg IFX-1 on days 1, 4, 8, 15 and the first two doses of 1600 mg IFX-1, which means that they will have experienced peak concentrations of IFX-1.

Criteria for the decision to proceed with enrolment in Arm A and to initiate enrollment in Arm B, will be based on assessment of general safety of IFX-1 treatment administration and with specific focus on occurrence of any of the following conditions:

- [redacted]

[redacted]

If any of these conditions occur in the first 3 patients treated with IFX-1 monotherapy, the steering committee will assess safety data and give recommendation on whether more patients should be enrolled into monotherapy Arm A before recruitment in Arm B may commence.

The steering committee will continue assessing the totality of safety information during the meetings scheduled for the review of the safety of the Combination Therapy Arm B.

5.3.2. Combination Therapy Arm B

In Arm B, during the safety run-in for each combination regimen cohort, the first 2 patients must be enrolled sequentially separated by a minimum of one week.

At the following time points, the Committee will review patient safety:

- For the very first patient receiving the combination therapy: After Cycle 1, Day 36, when this patient will have received the four consecutive IFX-1 fractionated loading dose administrations, one pembrolizumab administration, and two of the higher IFX-1 Q2W doses (to allow inclusion of subsequent patients)
- For each escalating dosing regimen: After 3 patients of each combination regimen cohort will have reached Cycle 1, day 36, at which they will have received the four consecutive IFX-1 fractionated loading dose administrations, one pembrolizumab administration, and two of the higher IFX-1 Q2W doses (to determine occurrence of DLT and necessity to include 3 more patients in a given dose cohort, to allow treatment in the next higher dose cohort, or to determine the MTD or RP2D)

To determine the RP2D, 6 patients should be treated at the MTD or highest dose level. If only 3 patients will have been enrolled into the respective cohort, 3 more patients will be enrolled at the same dose level. If no further toxicities are observed, this MTD will be selected as dose for Stage 2 and recommended combination regimen. Further patient enrollment in Arm B can proceed without specific rules.

The steering committee will continue to meet every three months until the last patient will have completed the third month of treatment in Stage 1 of the study and every six months thereafter to further confirm safety of the MTD or RP2D, and to further assess general safety of study treatment administration. All available safety data will be provided to the steering committee before each meeting.

5.4. Patient and Study Completion

This study plans to enroll a total of up to approximately 70 patients:

- Arm A (Phase II portion), Stage 1: 10 patients
- Arm A (Phase II portion), Stage 2: 19 patients
- Arm B (safety run-in): 12 to 18 patients (3 to 6 patients per regimen, out of which 6 patients must be treated at MTD or highest dose level)
- Arm B (Phase II portion), Stage 1: additional 4 patients (to reach the required 10 patients on the selected MTD or RP2D)
- Arm B (Phase II portion), Stage 2: 19 patients (to reach the total number of 29 patients on the selected combination dose)

In case none of the patients enrolled in Stage 1 of Arms A or B has a response evaluation of CR/iCR or PR/iPR, enrollment in the treatment arm can individually be stopped. All enrolled patients will be allowed to continue treatment until the end of treatment (EOT) criteria are met (see Sections 5.4.1 and 7.2.4); after the EOT Visit, they will proceed through the planned follow-up period (see Section 5.4.2) until end of study (EOS) (see Section 5.4.3).

5.4.1. End of Treatment Definition

EOT is defined as discontinuation of all study treatment administrations, i.e., IFX-1 alone or in combination with pembrolizumab treatment.

Discontinuation of study treatment does not represent withdrawal from the study.

An EOT Visit will be scheduled 30 days after last study treatment administration or before the patient starts on another antineoplastic therapy, whatever occurs earlier.

A patient, who discontinues study treatment administrations without progressive disease (PD)/confirmed PD (iCPD) will have tumor assessments at follow-up visits until PD/iCPD or start of subsequent antineoplastic therapy.

All patients will be followed for disease progression, survival status, and subsequent antineoplastic therapies as described in Section 5.4.2.

For details on treatment discontinuation criteria, see Section 7.2.4.

5.4.2. Follow-Up

Patients will be followed for survival and subsequent antineoplastic therapies every 3 months for 12 months after the EOT Visit. After the EOT Visit, tumor assessments will continue every 12 weeks until PD/iCPD or initiation of subsequent antineoplastic therapy for patients who discontinued study treatment for other reasons than progression. If required, information can be obtained by a phone call; a follow-up visit can be replaced by a phone call.

5.4.3. End of Study Definition

The EOS for the individual patient is defined as the date of the last contact of the 12 months follow-up period, date of death, date of consent withdrawal from study participation (see Section 5.4.4), or the date of last contact when patients are lost to follow-up (see Section 5.4.5).

The entire study will end when all patients have discontinued IFX-1 and IFX-1 + pembrolizumab treatment, AND all patients ended the study as described above.

The sponsor may prematurely terminate the study at any time earlier than planned for the following reasons:

- Unacceptable toxicity
- Administrative reasons

5.4.4. Consent Withdrawal/Discontinuation of Study Participation

A patient may withdraw from the entire study at any time at his/her own request without the need to provide any reason(s).

If the patient withdraws from study participation, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. Patients who wish to withdraw consent/discontinue the study while still on treatment should be encouraged by the investigator to perform the EOT Visit for their own safety before any further data collection for study purposes will be terminated. In such a case the EOS Visit information will be added to the EOT Visit information.

If a patient withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

5.4.5. Lost to Follow-Up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and the study site is unable to make contact as described below.

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

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

6. STUDY POPULATION

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

6.1. Inclusion Criteria

Type of Patients and Disease Characteristics

1. At least 18 years of age on day of signing informed consent
2. Patients with biopsy-proven, histologically or cytologically confirmed (a.) locally advanced cSCC not amenable for curative treatment or (b.) metastatic cSCC. Patients must have been treated with all approved therapies for (a.) inoperable locally advanced cSCC contraindicated for radiation therapy or (b.) metastatic cSCC. All patients to be included must have progressed on PD-1- or PD-L1-inhibitory antibody therapy.

a. <u>Locally advanced cSCC not amenable for curative treatment:</u>

Patients must have disease that is considered inoperable or medical contraindication to surgery or radiation or have not achieved disease control with these treatments.

Patients must have ≥1 measurable baseline lesion in which the longest diameter and the perpendicular diameter are both ≥10 mm on digital medical photography or that can be measured by CT/MRI as outlined in inclusion criterion 2b (metastatic cSCC).

Note: Non-measurable disease is defined as either uni-dimensionally measurable lesions, tumors with margins that are not clearly defined, or lesions with maximum perpendicular

diameters <10 mm. Patients without measurable disease at baseline are not eligible for the study.

- Surgery must be deemed contraindicated in the opinion of an expert in micrographics-controlled surgery (Moh's surgery, e.g., specifically trained dermatologic surgeon), a head and neck surgeon, or a plastic surgeon. A copy of the surgeon's consultation note from a clinical visit within 60 days of enrollment must be submitted. Acceptable contraindications in the surgeon's note include:
    - cSCC that has recurred in the same location after ≥2 surgical procedures and curative resection is deemed unlikely
    - cSCC with relevant local invasion that precludes complete resection
    - cSCC in anatomically challenging locations for which surgery may result in severe disfigurement or dysfunction (e.g., removal of all or part of a facial structure, such as nose, ear, or eye; or requirement for limb amputation)
    - Other conditions deemed to be contraindicating for surgery must be discussed with the medical monitor before enrolling the patient
- Patients must be deemed as not appropriate for radiation therapy. Specifically, patients must meet ≥1 of the following criteria:
    - A patient previously received radiation therapy for cSCC, such that further radiation therapy would exceed the threshold of acceptable cumulative dose, per the radiation oncologist. A copy of the radiation oncologist's consultation note, from a clinical visit within 60 days of enrollment, must be submitted.
    - Judgment of radiation oncologist that such tumor is unlikely to respond to therapy. A copy of the radiation oncologist's consultation note, from a clinical visit within 60 days of enrollment, must be submitted.
    - A clinic note from the investigator indicating that an individualized benefit-risk assessment was performed by a multidisciplinary team (consisting of, at minimum, a radiation oncologist AND EITHER a medical oncologist with expertise in cutaneous malignancies OR a dermato-oncologist, OR a head and neck surgeon) within 60 days prior to enrollment in the proposed study, and the radiation therapy was deemed to be contraindicated
- Acceptable contraindications to radiation therapy in the investigator's note for patients who have not received any prior radiation include:
    - cSCC in anatomically challenging locations for which radiation therapy would be associated with unacceptable toxicity risk in the context of the patient's overall medical condition in the opinion of the multidisciplinary team (e.g., a neck tumor

for which radiation therapy would result in potential need for a percutaneous gastrostomy tube). A copy of the investigator's consultation note documenting the multidisciplinary assessment must be submitted.

- Other conditions deemed to be contraindicating for radiation therapy must be discussed with the medical monitor before enrolling the patient.

- The diagnosis of cSCC must be confirmed in all patients with locally advanced cSCC by histopathological examination of archived or newly obtained tumor material (biopsy at screening) to be performed centrally by a sponsor-appointed cutaneous histopathologist. Treatment with the investigational drug must not commence prior to confirmation of the diagnosis. If archived tumor material is not available requiring a new biopsy for the confirmation of the diagnosis, it should be considered to obtain the mandatory biomarker biopsy at baseline (inclusion criterion 5) at the same time in order to avoid having to perform a second biopsy prior to the initiation of treatment. If the biopsies to confirm the diagnosis and to conduct the biomarker assessments are taken at the same time, it is important to obtain sufficient material to allow for the biomarker assessments (the equivalent of a 4 mm x 4 mm punch biopsy) in addition to the material required for the confirmation of the diagnosis. This can be achieved by either by taking a sufficiently large biopsy to be divided prior to fixation or by obtaining two biopsies.
- An investigator note which states that the natural history of the patient's advanced cSCC would likely be life-threatening within 3 years with currently available management options outside of a clinical study

b. Metastatic cSCC treated with all approved therapies for metastatic disease:

Patients are required to have histologic confirmation of distant cSCC metastases (e.g. lung, liver, bone, or lymph node). This confirmation of the diagnosis can be provided by a local investigator note based on the pathology review conducted locally.

Patients must have ≥1 baseline measurable lesion ≥10 mm in maximal diameter (1.5 cm in short axis for lymph nodes) according to RECIST v1.1 criteria (Appendix 3; Eisenhauer et al., 2009).

Note: In the case of a patient with metastatic disease that does not meet target lesion criteria by RECIST v1.1 criteria (e.g., bone only lesions, perineural disease) and with externally visible cSCC target lesions, Appendix 3 may be used, in which bi-dimensional measurements are required (at baseline, perpendicular diameters must both be ≥10 mm), after communication with and approval from medical monitor. The patient would then be enrolled with the plan to follow externally visible disease as target lesion(s), and metastatic lesions that are not measurable by RECIST v1.1 criteria may be followed as non-target lesions.

Note: There is no limit to the number of prior treatment regimens.

3. Patients must have progressed on treatment with an anti-PD1/L1 monoclonal antibody (mAb) administered either as monotherapy, or in combination with other checkpoint

inhibitors or other therapies. PD-1 treatment progression is defined by meeting all of the following criteria:

a. Has received ≥2 doses of an anti-PD-1/L1 mAb that has been approved for treatment of cSCC or any solid tumor

b. Has demonstrated PD/iCPD after PD-1/L1 inhibitor treatment as defined by RECIST v1.1/iRECIST. The initial evidence of disease progression is to be confirmed by a second assessment ≥4 weeks from the date of the first documented disease progression, unless there is rapid clinical progression.

c. Disease progression has been documented within 12 weeks from the last dose of anti-PD-1/L1 mAb.

4. The PD-1-/PD-L1 infusion must have been the most recent treatment for locally advanced or metastatic cSCC.

5. In addition to providing the material for ensuring the diagnosis as stated in inclusion criterion 2a for patients with locally advanced cSCC, patients must consent to undergo the following biopsies (at each time point a punch biopsy of externally visible cSCC lesions or a biopsy of material from accessible metastases) for biomarker assessments:

a. At baseline prior to the first administration of the investigational therapy and if possible, within 7 days prior to initiation of study treatment administration (mandatory for all patients)

b. For Stage 2 patients only: on Cycle 2 Day 1 (±3 days) (mandatory)

c. For Stage 2 patients only: at the time of CR/iCR/PR/iPR (optional, to be conducted only if the investigator considers this biopsy as clinically possible and potentially informative)

d. For Stage 2 patients only: At the time of tumor progression (optional, to be conducted only if the investigator considers this biopsy as clinically possible and potentially informative).

For all biopsies intended to analyze biomarkers, which needs to be the equivalent of a 4 mm x 4 mm punch biopsy. If biopsies for biomarkers are not feasible due to the complete absence of any suitable cutaneous or metastatic lesions, then this is not an exclusion criterion. However, this needs to be documented and confirmed by the investigator.

The biopsied lesion is not considered a target lesion.

6. Patients must have the following minimum washout before first study treatment administration from previous treatments:

a. ≥4 weeks for mAbs, systemic cytotoxic anticancer therapy, treatment with other anticancer investigational agents

b. ≥3 weeks for local radiation therapy

Note: Patients must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-central nervous system disease.

7. Eastern Cooperative Oncology Group performance status (ECOG PS) status of ≤1

8. Adequate organ function:

System	Laboratory Value
Hematological	
Absolute neutrophil count	≥1500/µL
Platelets	≥100 000/µL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Creatinine OR Measured or calculated[b] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥30 mL/min for patient with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 × ULN OR direct bilirubin ≤ULN for patients with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for patients with liver metastases)
Coagulation	
International normalized ratio OR PT aPTT	≤1.5 × ULN unless patient is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); aPTT=activated partial thromboplastin time; AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); CrCL=creatinine clearance; GFR=glomerular filtration rate; PT=prothrombin time; ULN=upper limit of normal.

a Hematology test should be obtained without transfusion or receipt of stimulating factors within 2 weeks before obtaining screening blood sample.
b CrCl should be calculated per institutional standard.

9. Patient (or legally acceptable representative if applicable) provides written informed consent for the study.

6.2. Exclusion Criteria

1. Patients with limited cSCC, who do not require systemic therapy
2. Has known active central nervous system metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided they are radiologically stable, i.e., without evidence of progression for ≥4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening),

clinically stable and without requirement of steroid treatment for ≥14 days prior to first dose of study treatment.

3. Has a diagnosis of immunodeficiency or autoimmune disease, or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 3 weeks prior the first dose of study treatment
4. Patients who have a history of (non-infectious) pneumonitis that required steroids or have current pneumonitis
5. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent, or with an agent directed to another stimulatory or co-inhibitory T cell receptor (e.g., cytotoxic T-lymphocyte-associated antigen 4, OX 40, CD137) and was discontinued from that treatment due to a ≥Grade 3 irAE
6. Has severe hypersensitivity (≥Grade 3) to pembrolizumab or IFX-1 and/or any of their excipients or had a severe (≥Grade 3) infusion-related reaction to treatments with other mAbs
7. Patients who fulfil inclusion criterion 6 (washout times) but who have not recovered from side effects of such therapies

Note: Patients must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline. Patients with ≤Grade 2 neuropathy may be eligible. If patients received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study treatment.

8. Has received a live vaccine within 30 days prior to the first dose of study treatment (see Section 7.4.1)
9. Patients who have undergone major surgery <4 weeks prior to starting study treatment
10. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study treatment

Note: Patients who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks after the last dose of the previous investigational agent.

11. Patients with known ≥Grade 3 (per NCI CTCAE v5.0 criteria) active systemic or cutaneous viral, bacterial, or fungal infection
12. Patients with known history of Hepatitis B or C infections or known to be positive for Hepatitis B antigen (HBsAg)/ Hepatitis B virus (HBV) DNA or Hepatitis C Antibody or RNA. Active Hepatitis C is defined by a known positive Hep C Ab result and known quantitative HCV RNA results greater than the lower limits of detection of the assay.
13. Patients who have a history of human immunodeficiency virus infection
14. Patients who have a history of interstitial lung disease
15. Patients who have had an allogeneic tissue/solid organ transplant
16. Patients with a history of other malignancies during the past 5 years.

Note: The following are exempt from the 5-year limit: curatively resected basal cell carcinoma, or carcinoma in situ (e.g., breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy.

17. Patients who are pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through [redacted] after the last dose of IFX-1 or 120 days after the last dose of pembrolizumab
18. Women of childbearing potential (WOCBP) who have a positive serum pregnancy test result within 7 days before treatment

Note: Post-menopausal women must be amenorrheic for ≥12 months to be considered not WOCBP (Appendix 7).

19. Male patients and WOCBP who do not agree to practice an effective method of contraception during study and [redacted] after last dose of IFX-1 or 120 days after last dose of pembrolizumab (Appendix 7)
20. Patients with congestive heart failure, Class III or IV, by New York Heart Association criteria
21. Patients with any serious underlying medical condition that would impair their ability to receive or tolerate the planned treatment
22. Patients with dementia or altered mental status that would preclude understanding and rendering of informed consent document

6.3. Screening Failures

Screening failures are defined as patients who are enrolled (i.e., consent to participate) in the clinical study but are not subsequently assigned to study treatment. A set of screen failure information will be collected and include demography, eligibility criteria, AE, and reason for screening failure.

Individuals who do not meet the criteria for participation in this study (screening failure) may be rescreened if failed eligibility criteria can only be corrected outside the first screening period.

6.4. Meals and Dietary Restrictions

Patients should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

7. STUDY DRUG(S) AND ADMINISTRATION

7.1. Investigational Medicinal Product

IMP is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study patient according to the study protocol.

7.1.1. IFX-1

7.1.1.1. Packaging and Labelling of Investigational Medicinal Product

IFX-1 concentrate for solution for infusion will be supplied in [redacted]mL glass vials at a concentration of[redacted]mg/mL ([redacted]mg per vial) for reconstitution and intravenous administration. Apart from IFX-1, the solution will contain sodium chloride, sodium phosphate, and polysorbate 80.

IFX-1 will be packaged in cartons and labeled in accordance with all legal requirements.

Each carton (or IMP kit) will be labeled with a unique number (IMP kit number). The glass vials containing IFX-1 will be labeled with the same medication number as the cartons in which they are packed.

Each carton and each vial will be labeled with a multilingual booklet label or a country specific single panel label as applicable.

7.1.1.2. Storage, Handling, and Accountability

Vials of IFX-1 must be stored [redacted]. All supplies of IFX-1 must be stored separately or segregated from other study supplies and site stock in a dedicated locked facility with access limited to authorized personnel. All storage facilities must be temperature controlled and monitored and compliant with applicable regulatory requirements.

An established and validated local temperature management system with temperature logs should be used to record the storage temperature. If this is not possible, the study site will be provided with a temperature record form by the Contract Research Organization and the site personnel will maintain temperature records for the entire duration of the study. At a minimum, the daily (working day) minimum and maximum temperatures must be documented.

Any deviation from the specified temperature range must be documented and reported within 24 hours (or the next working day). Further instruction on the management and reporting of temperature deviations is provided in the Pharmacy Manual.

The investigator or designee must confirm appropriate temperature conditions have been maintained during shipment for all IMP received and any discrepancies are reported and resolved before use of the IMP.

Only patients enrolled in the study may receive IMP and only authorized site staff may prepare and administer IMP. The IMP must be prepared in a controlled area in accordance with local regulations/requirements for reconstitution of products for intravenous administration; see Pharmacy Manual for more details.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for the correct storage of IMP, IMP accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused IMP are provided in the Pharmacy Manual.

7.1.1.3. Drug Preparation and Administration Instructions

The IFX-1 for infusion will be reconstituted (prepared) in a controlled area at the study site or at the study site's pharmacy, in accordance (compliance) with applicable local regulations/requirements for reconstitution of products for intravenous administration.

The reconstituted IFX-1 should be used within [redacted] hours after dilution when stored at room temperature. Otherwise, the reconstituted IFX-1 has to be stored at [redacted] and used within 24 hours; if the reconstituted IFX-1 solution is stored in a refrigerator, it must be left to acclimatize to room temperature prior to administration. Details on reconstituting the IFX-1 will be provided in the Pharmacy Manual.

The number of unused, partially used, and empty vials will be documented accurately, and the vials will be kept at the site until the drug accountability documentation has been checked by the study monitor.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7.1.1.4. Recall of Investigational Medicinal Product

Instructions (actions to be taken by site) in the case of IMP recall will be provided in the Pharmacy Manual.

7.1.2. Pembrolizumab

7.1.2.1. Packaging and Labelling of Investigational Medicinal Product

Pembrolizumab, 25 mg/mL concentrate for solution for infusion will be supplied as described in the Pharmacy Manual.

7.1.2.2. Storage, Handling, and Accountability

Storage conditions for pembrolizumab are described in the Pharmacy Manual.

An established and validated local temperature management system with temperature logs should be used to record the storage temperature. If this is not possible, the study site will be provided with a temperature record form by the Contract Research Organization and the site personnel will

maintain temperature records for the entire duration of the study. At a minimum, the daily (working day) minimum and maximum temperatures must be documented.

Any deviation from the specified temperature range must be documented and reported within 24 hours (or the next working day). Further instruction on the management and reporting of temperature deviations is provided in the Pharmacy Manual.

The investigator or designee must confirm appropriate temperature conditions have been maintained during shipment for all IMP received and any discrepancies reported and resolved before use of the IMP.

Only patients enrolled in the study may receive IMP and only authorized site staff may prepare and administer IMP. The IMP must be prepared in a controlled area in accordance with local regulations/requirements for reconstitution of products for intravenous administration

The investigator, institution, or the head of the medical institution (where applicable) is responsible for the correct storage of IMP, IMP accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused IMP are provided in the Pharmacy Manual.

7.1.2.3. Drug Preparation and Administration Instructions

The pembrolizumab for infusion will be reconstituted (prepared) in a controlled area at the study site or at the study site's pharmacy, in accordance (compliance) with applicable local regulations/ requirements for reconstitution of products for intravenous administration. Details on preparation and administration of pembrolizumab will be provided in the Pharmacy Manual.

The number of unused, partially used, and empty vials will be documented accurately, and the vials will be kept at the site until the drug accountability documentation has been checked by the study monitor.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7.1.2.4. Recall of Investigational Medicinal Product

Instructions (actions to be taken by site) in the case of IMP recall will be provided in the Pharmacy Manual.

7.2. Administration and Dosage

Patients will be openly assigned to either receive IFX-1 as monotherapy in treatment Arm A or IFX-1 in combination with pembrolizumab in treatment Arm B. IFX-1 will generally be administered 60 minutes (±10 minutes) post administration of pembrolizumab.

The first dose of IFX-1 is administered at Cycle 1 Day 1. The first dose of pembrolizumab is administered at Cycle 1 Day 8. Subsequent doses of IFX-1 and pembrolizumab may be administered up to 1 day before or after the scheduled day within the Cycle 1 and up to 3 days before or after the scheduled day of all following cycles due to administrative reasons.

To allow for a close observation of study treatment infusion(s), patients should remain at the study site for ≥60 minutes after end of infusion(s). Appropriate treatment for potential infusion-related reactions must be available during this time.

7.2.1. Treatment Administered

7.2.1.1. Monotherapy Arm A

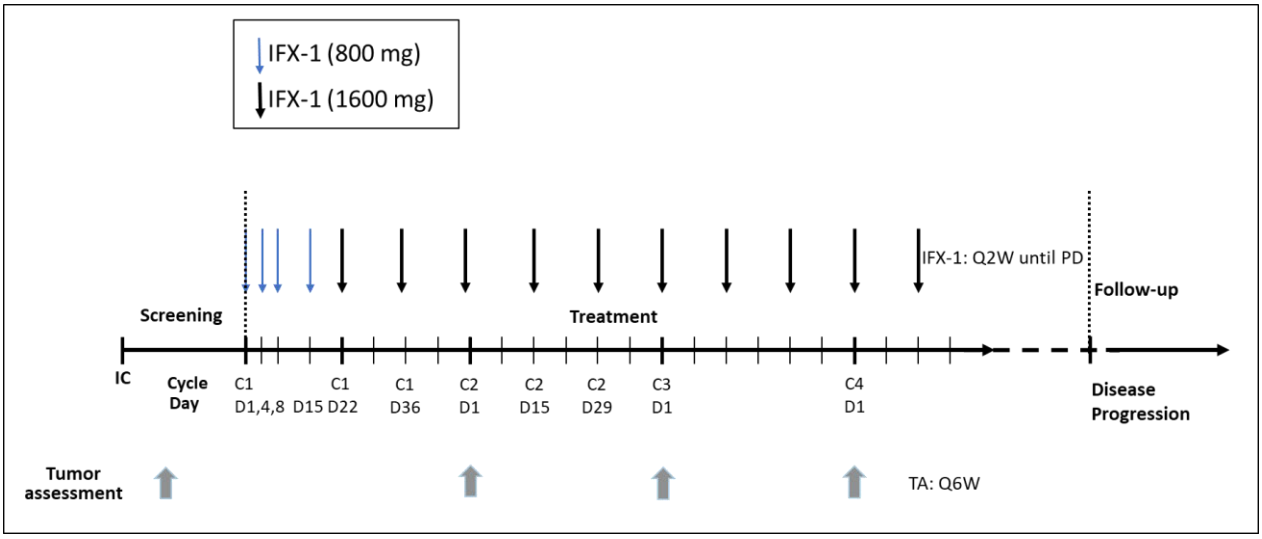
IFX-1 monotherapy will be administered as a 30-minute (-5/+10 minutes) intravenous infusion. Because of the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is allowed. Administrations will be given as follows (Figure 2):

- Cycle 1 Days 1, 4, 8, and 15: 800 mg IFX-1 (4 administrations).
- From Cycle 1 Day 22 on: 1600 mg IFX-1 Q2W until EOT (two administrations during Cycle 1 on Days 22 and 36 and 3 administrations per cycle on Days 1, 15, and 29 of Cycle 2 and all subsequent cycles).

Cycle 1 will comprise 7 weeks, whereas all following cycles will comprise 6 weeks of treatment.

Treatment will be continued until either disease progression is diagnosed, unacceptable toxicity occurred, or treatment has been administered for approximately 2 years.

Figure 2 Patient Calendar: Arm A (IFX-1 Monotherapy)



C: cycle; D: day; IC: informed consent; PD: progressive disease; Q2W: bi-weekly; Q6W: every 6 weeks; TA: tumor assessment.

7.2.1.2. Combination Therapy Arm B

As detailed in Section 5.1, Stage 1 of treatment Arm B consists of a safety run-in with patients being sequentially assigned to 1 out of 3 different escalating treatment regimens (Figure 3).

IFX-1 will be administered as a 30-minute (-5/+10 minutes) intravenous infusion as follows:

- Cycle 1: 400 mg (regimen 1), 600 mg (regimen 2), or 800 mg (regimen 3) IFX-1 (4 administrations on Days 1, 4, 8, and 15)
- From Cycle 1 Day 22 on:800 mg IFX-1 Q2W (regimen 1), 1200 mg IFX-1 Q2W (regimen 2), or 1600 mg IFX-1 Q2W (regimen 3) until EOT (2 administrations during Cycle 1 on Days 22 and 36 and 3 administrations per cycle on Days 1, 15, and 29 of Cycle 2 and all subsequent cycles)

IFX-1 treatment will be combined with pembrolizumab, starting at Cycle 1 Day 8 and then on Day 1 of each treatment cycle after all other procedures and assessments have been completed. IFX-1 infusion will start 60 minutes (±10 minutes) after the pembrolizumab infusion has been finished.

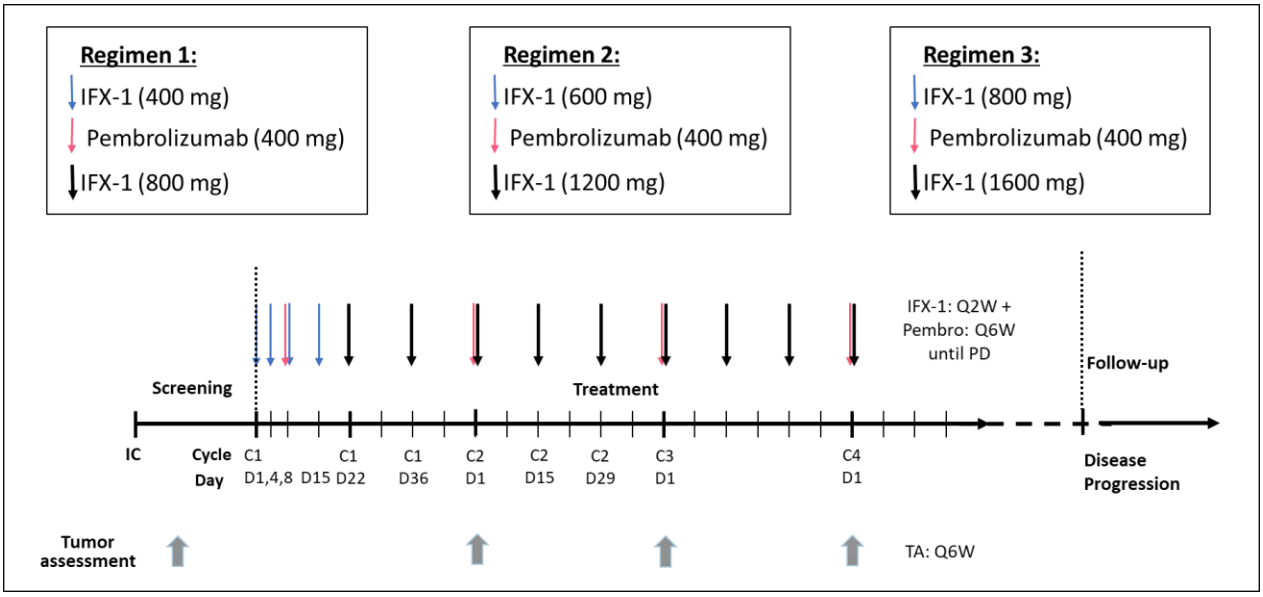
For those patients receiving less than 1600 mg IFX-1 Q2W (regimen 1 and 2) the dose of IFX-1 may be increased to 1600 mg Q2W at the discretion of the investigator after consultation of the sponsor as soon as the safety of this dose will have been confirmed in at least 3 patients receiving 1600 mg Q2W (regimen 3). This intrapatient dose escalation will only be allowed provided that patient has received at least 2 cycles of IFX-1 and had no Grade ≥ 2 treatment related adverse events.

Pembrolizumab will be administered as a 30-minute (-5/+10 minutes) intravenous infusion at a dose of 400 mg Q6W. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible.

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion and administration of infusion solution.

Treatment will continue until PD/iCPD or treatment discontinuation for any other reason (see Section 7.2.4) or treatment has been administered for approximately 2 years. If treatment will discontinue due to toxicity, continuation of either IFX-1 or pembrolizumab is allowed, given that the toxicity can be unequivocally attributed to 1 of the drugs (see Section 7.2.4.2).

Figure 3 **Patient Calendar: Combination Arm B (IFX-1 + Pembrolizumab)**



C: cycle; D: day; IC: informed consent; PD: progressive disease; Q2W: bi-weekly; Q6W: every 6 weeks; TA: tumor assessment.

3 more patients will be enrolled at the identified MTD or highest IFX-1 dose level (Regimen 3) in case only 3 patients have been previously treated in this dose cohort before it can be finally selected for Stage 2.

7.2.2. Treatment Modification

This protocol allows some alteration from the currently outlined dosing schedule, but a dose reduction of study treatment is generally not allowed. Patients treated in the safety run-in part of Arm B will be allowed to increase the assigned IFX-1 dose when the next higher dosing regimen was found to be safe by the steering committee (see Section 5.3.2). Increase to a higher than the planned highest dose, i.e., 800 mg QW as part of the fractionated loading dose on Cycle 1 Days 1, 4, 8, and 15 or 1600 mg Q2W from Cycle 1 Day 22 on, is not allowed and would require a protocol amendment.

All AEs leading to treatment modifications will be graded using NCI CTCAE v5.0 based on the investigator's assessment.

7.2.2.1. Monotherapy Arm A

In case of toxicity, IFX-1 dosing can be held by a maximum of 4 weeks. If therapy is continued during this time span, dosing will resume within the initial schedule and allowed administration window for a specific visit.

IFX-1 has the potential to elicit infusion-related reactions, including hypersensitivity or anaphylaxis. Treatment modification criteria due to infusion-related reactions are listed in Appendix 8, Table 5.

For treatment discontinuation criteria, see Section 7.2.4.

There are no DLTs defined for Arm A.

7.2.2.2. Combination Therapy Arm B

In case of toxicity, IFX-1 dosing can be held by a maximum of 4 weeks and pembrolizumab dosing by a maximum of 12 weeks. If therapy is continued during this time span, dosing will resume within the initial schedule and allowed administration window for a specific visit.

For treatment modifications due to irAEs, see Section 7.2.2.2.1 and due to infusion-related reactions, see Section 7.2.2.2.2.

IFX-1 and pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical/surgical events or logistical reasons not related to study therapy. However, pembrolizumab is to be restarted within 6 weeks or 42 days of the originally scheduled dose and within 12 weeks or 84 days of the previously administered dose, unless otherwise discussed with the Sponsor. IFX-1 is to be restarted within 2 weeks or 14 days of the originally scheduled dose and within 4 weeks or 28 days of the previously administered dose. The interruption shall not lead to a longer dosing interval than 4 weeks for IFX-1 and 12 weeks for pembrolizumab. The reason for interruption should be documented in the patient's study record.

For treatment discontinuation criteria, see Section 7.2.4.

7.2.2.2.1. Immune-Related Adverse Events

AEs associated with pembrolizumab exposure may represent an immune-related response. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids, and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, and skin biopsy may be included as part of the evaluation. Dose modification criteria for pembrolizumab in response to Grade 2 or higher irAEs are listed in

Appendix 8, Table 4. If treatment should be withheld due to toxicity, both pembrolizumab and IFX-1 should be withheld (see Appendix 8, Table 4).

7.2.2.2.2. Infusion-Related Reactions

IFX-1 as well as pembrolizumab may cause severe or life-threatening infusion-related reactions, including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification criteria for infusion-related reactions are listed in Appendix 8, Table 5.

7.2.2.2.3. Dose-Limiting Toxicities

DLTs are only defined for combination Arm B. All DLTs will be graded using NCI-CTCAE Version 5.0 based on the investigator assessment.

A DLT is a toxicity that occurs during the DLT assessment period up to and including Cycle 1 treatment day 36 and is assessed by the investigator as being possibly, probably, or definitely related to study treatment administration. DLTs are defined by the following:

1. Nonhematologic toxicity (not laboratory):
   - Drug related Grade 3 or 4 infections and infestations
   - Any treatment-related toxicity that causes the patient to discontinue treatment; see Appendix 8, Table 4 for dose modification criteria in case of irAEs, and Table 5 in case of infusion-related reactions
2. Grade 4 hematologic toxicity lasting ≥7 days, except thrombocytopenia:
   - Grade 4 thrombocytopenia of any duration
   - Grade 3 thrombocytopenia associated with clinically significant bleeding that may require transfusion, invasive intervention, or hospitalization
3. Any nonhematologic AE ≥Grade 3 in severity should be considered a DLT, with the following exceptions: Grade 3 fatigue lasting ≤ 3 days; Grade 3 diarrhea, nausea, or vomiting without use of anti-emetics or anti-diarrheals per standard of care; Grade 3 rash without use of corticosteroids or anti-inflammatory agents per standard of care.
4. Any Grade 3 or Grade 4 non-hematologic laboratory value if:
   - Clinically significant medical intervention is required to treat the participant or
   - The abnormality leads to hospitalization, or

- The abnormality persists for >1 week.
- The abnormality results in a Drug-induced Liver Injury (DILI)

5. Febrile neutropenia Grade 3 or Grade 4:
   - Grade 3 is defined as ANC <1000/mm^3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than 1 hour
   - Grade 4 is defined as ANC <1000/mm^3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than 1 hour, with life-threatening consequences and urgent intervention indicated.
6. Prolonged delay (>2 weeks) in initiating Cycle 2 due to treatment-related toxicity.
7. Any treatment-related toxicity that causes the participant to discontinue treatment during Cycle 1.
8. Missing >25% of 1 or both IND doses (IFX-1 and/or pembrolizumab) doses as a result of drug-related AE(s) during the first cycle.
9. Grade 5 toxicity.

The frequency, time to onset, and severity of toxicities, as well as the success of standard medical management and dosing interruptions/delays, will be analyzed to determine if a given toxicity should be considered a DLT for dose escalation purposes.

TEAEs that appear to meet the DLT definition will be discussed between the investigator, the sponsor and the steering committee (see Section 5.3.2). The final decision of whether or not the AE meets the DLT definition will be based on a careful review of all relevant data and consensus between the investigator, sponsor, and steering committee.

7.2.2.2.4. Maximum Tolerated Dose

The MTD is defined as the highest dose at which ≤1 of 3 patients or ≤1 of 6 patients (in an expanded cohort) experience a DLT with IFX-1 in combination with 400 mg pembrolizumab. Thus, the MTD is defined as the dose level immediately below the level at which dosing is stopped due to the occurrence of >1 DLT in a cohort with 3 patients or of >1 DLT in an expanded cohort of 6 patients. If dose escalation is not stopped due to the occurrence of DLTs, it will be considered that the MTD has not been determined and the highest IFX-1 dose level will be considered as dose for Stage 2. 6 patients will need to be treated at the MTD or at the highest IFX-1 dose level (Regimen 3, if MTD was not reached) to decide if this dose can be selected as RP2D which will then be explored in the Phase II portion of Arm B. In case only 3 patients will have been previously treated at the MTD or highest IFX-1 dose level, 3 more patients will be added to this cohort. If 6 patients were already treated at the proposed dose level, then additional patients will not be required and the decision on the RP2D will be made based on the available data.

7.2.3. Re-Dosing Criteria

The following criteria must be fulfilled to allow for re-dosing of study treatment:

- Absence of treatment discontinuation criteria (see Section 7.2.4)
- AEs fulfilling DLT criteria (see Section 7.2.2.2.3) must have been reviewed by the steering committee (see Section 5.3.2) and found not to be limiting.
- Any other Grade 3 or higher AEs have to improve to Grade 1 or baseline OR a Grade 3 AE can be managed and stabilized by supportive/medical therapy, e.g., Grade 3 hypertension can be controlled by addition of a second antihypertensive medication and should improve to Grade 1 or baseline.

7.2.4. Treatment Discontinuation Criteria

Discontinuation of study treatment does not represent withdrawal from the study. See Section 5.4.1 for the EOT definition and procedures at EOT Visit.

Patients should be treated with IFX-1 or the IFX-1+pembrolizumab combination until disease progression or unacceptable toxicity occurs or treatment has been administered for approximately 2 years. With Sponsor agreement, drug administration can continue for patients with initial evidence of PD according to RECIST v1.1 (Eisenhower et al., 2009) but are clinical stable in line with the concept of unconfirmed PD (iUPD) according to iRECIST criteria (Seymore et al., 2017).

For the purpose of this decision process, lack of clinical stability is defined as:

- Unacceptable toxicity
- Clinical signs or symptoms indicating clinically significant disease progression
- Decline in performance status

Rapid disease progression or threat to vital organs or critical anatomical sites (eg, CNS metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention.

7.2.4.1. Monotherapy Arm A

Possible reasons for treatment discontinuation for individual patients are:

- PD/iCPD
- Clinical deterioration
- Non-compliance with protocol procedures
- Study participation consent withdrawal (see Section 5.4.4)
- Pregnancy
- Safety:

- Grade 2 infusion-related reactions despite adequate premedication (see Appendix 8, Table 5)
- Grade 3 or 4 infusion-related reactions (see Appendix 8, Table 5)

7.2.4.2. Combination Therapy Arm B

Possible reasons for treatment discontinuation for individual patients are:

- PD/iCPD
- Clinical deterioration
- Non-compliance with protocol procedures
- Study participation consent withdrawal (see Section 5.4.4)
- Pregnancy
- Safety:
  - Any study intervention-related toxicity (immune-related adverse events or infusion-related reactions) specified as a reason for permanent discontinuation as defined in the guidelines for dose modification due to AEs (see Appendix 8, Table 4, Table 5)
- Discontinuation of pembrolizumab treatment may be considered for patients who have attained a confirmed CR and have received ≥2 doses of pembrolizumab beyond the date when the initial CR was declared
- Discontinuation of pembrolizumab treatment may be considered after completion of 18 cycles (approximately 2 years) with pembrolizumab

Upon occurrence of any TEAE that, in the opinion of the investigator, is solely related to either IFX-1 or pembrolizumab, continuation of treatment with the other combination partner alone is possible but requires sponsor agreement. In case of specific IFX-1 toxicities pembrolizumab may be continued as a monotherapy for approximately 2 years.

7.3. Premedication and Postmedication

Routine premedication is not required prior to the first dose of IFX-1 or pembrolizumab.

Patients with mild or moderate infusion reaction following IFX-1 or pembrolizumab administration may continue to receive IFX-1 or pembrolizumab with close monitoring; premedication with antipyretic and antihistamine may be considered.

Patients should be observed in the treatment facility for 60 minutes, or longer per clinical judgment, after study treatment administrations.

Treatment guidelines are detailed in Appendix 8, Table 5.

7.4. Concomitant Medication/Treatments

Any medication or treatment that the patient is receiving within 28 days prior to the first dose of study treatment and up to 30 days after the last dose should be recorded.

For details, please see Section 8.1.4.

7.4.1. Prohibited Concomitant Medication/Treatment

Medications or vaccinations specifically prohibited in the exclusion criteria (see Section 6.2) are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study therapy or vaccination may be required. The investigator should discuss any questions regarding this with the medical monitor. The final decision on any supportive therapy or vaccination rests with the investigator and/or the patient's primary physician. However, the decision to continue the patient on study treatment requires the mutual agreement of the investigator, the sponsor, and the patient.

The following concomitant therapies or vaccinations are prohibited during the course of the study:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab and IFX-1
- Radiation therapy
- Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, Bacillus Calmette-Guérin, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed. See exclusion criterion #8.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an AE that is suspected to have an immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the sponsor.

  Note: Inhaled steroids are allowed for management of asthma.

Patients who, in the assessment of the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study.

All treatments that the investigator considers necessary for a patient's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care.

7.5. Rescue Medications and Supportive Care

Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 7.2.2 and Appendix 8, Table 4. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the investigator does not need to follow the treatment guidance.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

7.6. Treatment of Overdose

No specific information is available on the treatment of overdose of pembrolizumab or IFX-1. For this study, an overdose of pembrolizumab will be defined as any dose of ≥1000 mg. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

In the event of an overdose, the investigator should:

1. Contact the medical monitor immediately
2. Closely monitor the patient for any AE/SAE and laboratory abnormalities
3. Report the overdose (IFX-1 only symptomatic, pembrolizumab symptomatic and asymptomatic overdoses) in accordance with the Section 9.2 through the SAE page in the eCRF. Document the actually delivered dose of the IMP as well as the duration of infusion in the eCRF SAE page (narrative section) within **24 hours** of event occurrence.
4. In addition, document the actual dose added to the infusion bag, the duration of the infusion, and the actually delivered dose on the respective IMP administration pages in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the patient.

8. STUDY ASSESSMENTS AND PROCEDURES

Patient consent will be obtained prior to performance of any study related procedures; standard of care procedures applicable to screening obtained within 28 days of first drug administration (or

clearly medically relevant for this period, as agreed by the sponsor,) can be used for qualification unless otherwise specified.

Study procedures and their timing are summarized in the SoA (Table 1) and further detailed per study period and visit in Appendix 1.

Details on the assessments and procedures are given in the following subsections.

Safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue any study treatment.

Adherence to the study design requirements, including those specified in the SoA (Table 1), is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria (Sections 6.1 and 6.2). An eligibility form will be used to enable the sponsor to agree on inclusion and assignment to a treatment arm. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

For details on the amount of blood collected from each patient over the duration of the study, see Laboratory Manual.

8.1. Baseline Assessments

The following procedures will be performed to assess baseline characteristics during screening evaluations and before study treatment administration:

- Documentation of demographic details (age, gender, race, and ethnicity), medical and disease history (see Sections 8.1.1 and 8.1.2)
- Disease assessments (see Section 8.2 and Appendix 3)
- QoL/EORTC (see Section 8.8)
- Documentation of concomitant disease and prior and concomitant medications (see Sections 8.1.3 and 8.1.4)
- Baseline safety assessment (height, weight, physical exam, vital signs, electrocardiogram (ECG), AEs, and safety laboratory; see Section 8.3)
- Skin or metastasis biopsy (if skin biopsy is not possible) for biomarker assessments (see Section 8.6)
- Baseline assessment of pharmacodynamic parameters (C3a, C5a, ADA) and PK

8.1.1. Medical History (Except cSCC History)

The documentation of the patient's medical history includes any details on the patient's medical history before enrollment into the study. The information must be documented as such in the source documentation and eCRF.

8.1.2. cSCC (Disease) History

Any details on the patient's cSCC disease history including any cSCC therapy (surgery, systemic therapy, radiation therapy by verbatim name with start and end dates, dosages) that the patient received will be documented in the source documentation and in the eCRF.

8.1.3. Concomitant Disease

All ongoing diseases diagnosed prior to enrollment into the study are regarded as concomitant diseases. All concomitant diseases must be documented in the patient file and in the eCRF.

8.1.4. Prior and Concomitant Medication/Treatments

All prior anticancer medication irrespective of the time of treatment and any medication or vaccine (including over the counter or prescription medicines, vitamins, and/or herbal supplements) that the patient is receiving within 28 days prior to the first dose of study treatment and up to 30 days after the last dose should be recorded in the patient file and in the eCRF along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose, route and frequency

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

In case of SAEs occurring later than 30 days after the last dose of study treatment, respective concomitant medications administered should be recorded.

8.2. Efficacy Assessments

Tumor assessments and response evaluation will be done per modified RECIST v1.1 (Eisenhauer et al., 2009) followed by iRECIST. iRECIST introduces additional tumor assessment and response evaluation criteria at time of a first response evaluation of PD according to RECIST v1.1, to accommodate for situations where a pseudo-progression is suspected (Seymore et al., 2017). Tumor assessments, using adequate imaging techniques including standardized medical photography, and response evaluation will be performed and documented after every cycle throughout the study. In case patients experience a PR/iPR or CR/iCR that lasts ≥1 year, imaging frequency can be decreased to every other cycle. For further details see Appendix 3. Independent

response evaluation could be initiated by the sponsor any time during the study. In preparation of a conditional, result-driven independent response evaluation, copies of all tumor assessment images will be collected.

8.2.1. Imaging Requirements

Medical photography and computed tomography (CT) or magnetic resonance imaging (MRI) for tumor assessment will be performed locally at each scheduled tumor assessment time point (after every cycle), and at any time when disease progression is suspected.

Note: after a response evaluation of PD/iCPD while on study treatment, additional scans are not required at scheduled follow-up visit procedures.

The choice of whether the imaging is by CT or MRI is an investigator decision (see Appendix 3). Once the choice has been made to use CT scan or MRI, subsequent assessments should be made using the same modality whenever possible.

8.2.2. Evaluation of Overall Response

The best overall response is the best response recorded from the start of the study treatment until EOT or documentation of disease progression according to RECIST v1.1/iRECIST (PD/iCPD). The patient's best overall response assignment will depend on the findings of both target and non-target disease, appearance and size of new lesions, and clinical stability (see Appendix 4). For patients discontinuing treatment for other reasons than PD/iCPD, the tumor assessments will continue during the follow-up period (also see the SoA, Table 1).

8.3. Safety Assessments

Safety will be assessed based on the following variables:

- AEs (see Section 9 and Section 8.3.1)
- Laboratory safety parameters and pregnancy test (see Section 8.3.2)
- Vital signs (see Section 8.3.3)
- ECG (see Section 8.3.4)
- Physical examination, ECOG PS (see Section 8.3.5)
- Immunogenicity/IFX-1 ADA status (see Section 8.3.6)

Planned time points for all safety assessments are provided in the SoA (Table 1).

8.3.1. Adverse Events Assessments

AEs will be assessed throughout the study from informed consent to EOS at each study visit. For details on AE collection and reporting, see Section 9. The investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned

to normal, or until progression has been stabilized, or until death, in order to ensure the safety of the patients. This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the sponsor. When study treatment is prematurely discontinued, the patient's observation will continue until the EOS for that patient.

8.3.2. Clinical Safety Laboratory Assessments

Blood samples for safety laboratory analysis should be obtained after the patients have provided responses to QoL questionnaire and after vital signs assessments have been performed, but before administration of study treatment.

See Appendix 2 for the list of clinical laboratory tests to be performed and the SoA (Table 1) for timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes (clinically relevant abnormal findings) occurring during the study in the AE section of the eCRF. The laboratory reports must be filed in the patient file. Clinically relevant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition.

All laboratory tests with values considered clinically relevantly abnormal occurring until 30 days after EOT should be reported in the AE section of the eCRF and repeated until the values return to normal or baseline, are no longer considered clinically relevant by the investigator or medical monitor, or until the EOS (also see Section 9 and Appendix 6).

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the SoA (Table 1).

If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in patient management or are considered clinically relevant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the eCRF.

For details on pregnancy testing, refer to Appendix 7.

8.3.3. Vital Signs

Core body temperature, heart rate, respiratory rate, and blood pressure (diastolic and systolic) will be assessed at each visit at pre-dose, and H0+1h (±5 minutes), where H0 is the beginning of IFX-1 administration, on the days of study treatment administration and at further time points whenever medically indicated.

Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Vital signs will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse and respiratory rate.

8.3.4. Electrocardiograms

Triplicate 12-lead ECG will be obtained as outlined in the SoA (Table 1) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and corrected QT (QTc) intervals.

At each ECG time point triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but ≤2 minutes apart. The full set of triplicates should be completed in <4 minutes.

The ECG should be performed at screening, on Cycle 1 Day 1 pre-dose and at H0+1 (±5 minutes), on Cycle 2 Day 1 at H0+1 (±5 minutes), and at the EOT Visit.

8.3.5. Physical Examination

A physical examination will be conducted at screening and each study visit.

The physical examination includes, at a minimum, assessments of the skin, cardiovascular, respiratory, gastrointestinal, and neurological systems. Height (at screening) and weight will also be measured and recorded, and ECOG PS must be assessed and documented (Appendix 9).

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

8.3.6. Immunogenicity

Serum immunogenicity samples will be collected from all patients at time points specified in the SoA (Table 1). The ADA assays for IFX-1 will be performed by a bioanalytical laboratory under the responsibility of the sponsor. These assays and analysis methods will be defined in a Bioanalytical Protocol and the results will be included in a Bioanalytical Report.

8.3.7. Survival Status

The patient survival status will be assessed during follow-up and will be documented in the eCRF. In case the patient has died, and the date of death is unknown, the date of the last personal contact should be documented at a minimum.

8.3.8. Antineoplastic Therapies

Any antineoplastic therapy or medication administered to the patients after completion or discontinuation of study treatment administration until EOS must be documented in the patient file

and eCRF with details on the date(s) of administration (with start and end dates), and dosing information, including dose, route, and frequency of administration.

8.4. Pharmacokinetics

Samples will be used to evaluate the PK of IFX-1.

Plasma samples will be collected for measurement of plasma concentrations of IFX-1 as specified in the SoA (Table 1).

Additional samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. Instructions for the collection and handling of biological samples will be provided in the Laboratory Manual. The actual date and time (24-hour clock time) of each sample will be recorded.

8.5. Pharmacodynamics

Venous blood samples will be collected for measurement of C3a and C5a at the time points specified in the SoA (Table 1) pre-dose.

8.6. Explorative Biomarkers

Tumor samples will be taken in order to characterize the tumor and its tumor microenvironment (TME) and to evaluate association of TME characteristics with the observed clinical responses to IFX-1. These biopsies (punch biopsies of externally visible cSCC lesions or biopsies of material from accessible metastases) are to be obtained at the following time points:

a. At baseline, prior to the first administration of the investigational therapy and if possible, within 7 days prior to initiation of study treatment administration (mandatory for all patients)

b. For Stage 2 patients only: on Cycle 2 Day 1 (±3 days) (mandatory)

c. For Stage 2 patients only: at the time of CR/iCR/PR/iPR (optional, to be conducted only if the investigator considers this biopsy as clinically possible and potentially informative)

d. For Stage 2 patients only: At the time of tumor progression (optional, to be conducted only if the investigator considers this biopsy as clinically possible and potentially informative).

For all biopsies intended to analyze biomarkers, it is important to obtain sufficient material to conduct the biomarker program, which needs to be the equivalent of a 4 mm x 4 mm punch biopsy. If biopsies for biomarkers are not feasible due to the complete absence of any suitable cutaneous or metastatic lesions, then this is not an exclusion criterion for enrollment into the study. However, the fact that a mandatory biopsy was not possible needs to be clearly documented and justified by the investigator.

Sampling must be obtained at minimal clinical risk from a skin lesion that has not been previously irradiated and that does not represent target lesions for response assessment. Detailed sampling instructions will be provided in the Laboratory Manual.

Explorative biomarker analyses will include tissue-based biomarkers in skin-based tumor lesions, before and during IFX-1 administration

In addition, samples will be stored and analysis may be performed on biomarker variants thought to play a role in development of cSCC or mode of action of the studied drug(s) including, but not limited to specific candidate genes, genome-wide analysis for RNA, plasma/serum analytes, or tissue biomarkers.

Other samples (e.g., unused samples collected for ADA assessments) may be used for research to develop treatments, methods, assays, prognostics, and/or companion diagnostics related to potential complement driven diseases.

Further instructions regarding the collection, processing, and shipping of samples for central analysis will be available in the Laboratory Manual.

8.7. Genetics

Germline genetic samples will not be obtained during this study.

8.8. Quality of Life (EORTC-QLQ-C30)

The EORTC-QLQ-C30 was designed to measure cancer patients' physical, psychological and social functions. The questionnaire is composed of 5 multi-item scales (physical, role, social, emotional, and cognitive functioning) and 9 single items (pain, fatigue, financial impact, appetite loss, nausea/vomiting, diarrhea, constipation, sleep disturbance, and QoL) (available at https://qol.eortc.org/questionnaire/eortc-qlq-c30/). The EORTC-QLQ-C30 will be provided to the sites.

8.9. Health Economics

Health Economics are not evaluated in this study.

9. ADVERSE EVENT COLLECTION AND REPORTING

AEs will be documented in the patient files, and reported via the eCRF, including a seriousness assessment (see Appendix 6 I). SAE reports (on paper only if the eCRF is unavailable, see Appendix 6 II) will be processed by the safety vendor (see Section 9.2.1). The safety vendor for this study is IQVIA Pharmacovigilance (see Appendix 10 for details on external responsibilities). Instructions for AE reporting are provided by the eCRF completion guidelines.

The investigator is responsible for detecting, documenting, recording, and following up on events that meet the definition of an AE and remains responsible for following up on AEs considered related to the study treatment or to study procedures (see Section 9.3 and Appendix 6 II), or that caused the patient to discontinue study treatment (see Section 7.2.4) or study participation.

AE records describe the diagnosis (alternatively signs and symptoms), seriousness, severity (NCI CTCAE v5.0 grading), start date and time, stop date and time, actions taken with respect to the study treatment, corrective treatment/therapy given, additional investigations performed, outcome, and the relationship to study treatment (see Section 9.3).

Terms like “disease progression” or “progressive disease”, do not sufficiently describe the nature of an AE. For example, if a patient is hospitalized for disease progression with hemoptysis, the investigator needs to report an AE and SAE for the hemoptysis. Data related to disease progression should be captured in the tumor assessment and response evaluation section of the eCRF.

9.1. Duration of Adverse Event Collection and Reporting

The following timeframes for reporting apply:

9.1.1. Non-serious Adverse Events

- All non-serious AEs must be reported from patient's informed consent until 30 days following discontinuation of study treatment
- All AEs must be followed until the outcome of the event is “recovering” (for stabilization of chronic conditions), or recovered (/with sequelae), and until all queries related to these AEs have been resolved.
- Ongoing AEs should be reviewed at each visit until EOT Visit or study discontinuation. If resolved, the details should be recorded in the eCRF.
- All ongoing AEs at the EOT Visit will have to be followed up until the outcome of the event is “recovering” (for chronic conditions), or recovered, until the EOS visit and until all queries related to these AEs have been resolved.
- If during an AE period, changes for the worse, in frequency of episodes/symptoms or in severity are observed, the final AE entry/report must include the maximum severity and frequency observed for this AE.
- If the patient dies from an event, ongoing AEs can be closed with an outcome “not known” if the outcome was not re-assessed at the day of death.

9.1.2. Adverse Events of Special Interest (AESI)

- All AESIs must be reported from first study drug administration until 30 days following discontinuation of study treatment. Please see Section 9.7 for the definition of AESIs.

9.1.3. Serious Adverse Events

- All SAEs from patient's informed consent on until 90 days following discontinuation of study treatment must be reported
- All related SAEs must be followed until resolution, death, loss to FU or EOS
- SAEs related to study treatment with onset during the follow-up period (from the EOT Visit until the EOS) will have to be collected and followed until resolution.
- After the EOS, only new SAEs related to study treatment must be reported to the sponsor.

9.1.4. Pregnancies

- All pregnancies from the time of treatment allocation until [redacted] after the last dose of IFX-1 or 120 days after the last dose of pembrolizumab, whichever is later, must be reported by the investigator as described in Section 9.6.2.
- If the patient initiates new anticancer therapy after discontinuation of the study treatment, pregnancy must be reported until 30 days following discontinuation of the study treatment, as described in Section 9.6.2.

9.1.5. Breastfeeding

- All exposures during breastfeeding from the time of treatment allocation until [redacted] after the last dose of IFX-1 or 120 days after the last dose of pembrolizumab, whichever is later, must be reported by the investigator as described in Section 9.6.2.
- If the patient initiates new anticancer therapy after discontinuation of the study treatment, exposure during breastfeeding must be reported until 30 days following discontinuation of the study treatment, as described in Section 9.6.2.

9.2. Serious Adverse Event Reporting and Timelines

9.2.1. Initial Reporting of Serious Adverse Events

All SAEs should be reported within 24 hours in the SAE section of the eCRF and approved by the investigator (see Appendix 6 II). Subsequent to an immediate automatic alert, triggered by the eCRF system, the SAE report will be processed by the safety vendor. In addition, SAEs need to be reported in the (non-serious) AE section of the eCRF. The investigator is obligated to provide all information of the event that is available at the time of the initial contact.

In case of disturbed or interrupted access to eCRF, please use the following FAX line or e-mail account for submission of SAEs (related/unrelated):

Fax: +353 1 809 9501

QLS_IFX1@iqvia.com

In addition, care should be taken to ensure that the patient's identity is protected and the patient identifier in the clinical study are properly mentioned on any copy of a source document provided to the sponsor. If laboratory results are provided, they must be supplemented by laboratory normal ranges.

9.2.2. Follow-Up Reporting of Serious Adverse Events

Follow-up information on SAEs must be reported by the investigator within the same time frames as the initial reporting.

A follow-up report to an SAE should be prepared if any relevant change in the patient's medical condition occurs, or any new relevant information becomes available.

Further information on follow-up procedures is given in Appendix 6.

9.3. Determination of Relationship

The investigator will use medical consideration to determine the relationship of an AE to study treatment based on the following definitions (see also Appendix 6 II):

Unrelated

This category applies to AEs that are due to extraneous causes (disease, concomitant medication, environment, etc.) and are not related to study treatment.

Unlikely Related

This category applies to AEs that are unlikely related to study treatment. The relationship of an AE to study treatment can be considered unlikely related if (must have at least 2 criteria listed below):

- The AE does not follow a reasonable temporal sequence from administration of the drug
- The AE could readily have been a result of the patient's clinical state or other underlying medical condition, environmental or toxic factors, or other modes of therapy administered to the patient
- The AE does not follow a known response pattern to the suspected drug
- The AE does not reappear or worsen when study treatment is re-administered

Possibly Related

This category applies to AEs that are unlikely to be related to the administration of study treatment, but the possibility cannot be ruled-out with certainty. The relationship of an AE to study treatment can be considered possibly related if (must have at least 2 criteria listed below):

- The AE follows a reasonable temporal sequence from administration of study treatment

- The AE could readily have been a result of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient
- The AE follows a known response pattern to the suspected study treatment

Probably Related

This category applies to AEs that are considered with a high degree of certainty to be related to study treatment. The relationship of an AE to study treatment can be considered probably related if (must have at least 3 criteria listed below):

- The AE follows a reasonable temporal sequence from administration of study treatment
- The AE could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient
- The AE disappears or decreases upon discontinuation of study treatment or reduction in dose
- The AE follows a known response pattern to the suspected study treatment

Definitely Related

This category applies to AEs that are determined with certainty to be related to study treatment. The relationship of an AE to study treatment can be considered definitely related if (must have at least 3 criteria listed below):

- The AE follows a reasonable temporal sequence from administration of study treatment or study treatment levels have been established in body fluids or tissues
- The AE could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient
- The AE disappears or decreases upon discontinuation of study treatment or reduction in dose and, if applicable, appears upon re-challenge
- The AE follows a known response pattern to the suspected study treatment
- There are exceptions when an AE does not disappear upon discontinuation of study treatment, yet study treatment relatedness clearly exists; e.g., 1) tardive dyskinesia, 2) fixed drug eruptions

9.4. Death Reporting

The site should follow all patients for survival and collect information around the death on the appropriate eCRF form until the end of the study.

Primary cause of death should be reported in AE section and SAE form, as well as appropriate eCRF section(s). If symptoms of disease progression occurred and constitute the primary cause of death, these symptoms could be reported as fatal (S)AE (see Section 9.3).

9.5. Abnormal Laboratory Values/Vital Signs/Electrocardiogram/Physical Examination

Abnormalities of Laboratory results/vital signs/ECG/physical examination should be reported as AEs (using the NCI CTCAE v5.0 terminology) particularly if ≥1 of the following is met:

- Any criterion for an SAE is fulfilled
- The abnormality causes the patient to discontinue from the study treatment.
- The abnormality causes the patient to interrupt the study treatment or a modification of dosing.
- The abnormality requires intervention as corrective treatment or consultation.
- The investigator judges that the abnormality is clinically relevant and should be reported as an (S)AE in the eCRF.

All laboratory tests for which abnormal results are collected after the initiation of study treatment should be repeated until the values return to normal or to a stable status. All abnormal results are assessed as clinically relevant by the investigator must be reported as an AE. The frequency of such checks is at the investigator's discretion depending on the degree of abnormality. The reporting of laboratory/vital signs/ECG/physical examination abnormalities (e.g., anemia) as both AEs and a specific finding of laboratory values/vital signs/ECG (e.g., decrease in red blood cells) should be avoided.

9.6. Events to be Handled as Serious Adverse Events

9.6.1. Overdose Reporting

An overdose is defined as the accidental or intentional ingestion or infusion of any dose of a product that is considered both excessive and medically relevant.

Generally, overdoses should be handled as SAEs and should be reported via the eCRF SAE page. In case of an asymptomatic overdose for IFX-1, please do not report it as serious AE.

These steps must be followed:

1. Report the overdose (IFX-1: only symptomatic; pembrolizumab: symptomatic and asymptomatic overdoses) in accordance with the Section 9.2 through the SAE page in eCRF. Document the actually delivered dose of the IMP as well as the duration of infusion in the eCRF SAE page (narrative section) within **24 hours** of event occurrence.
2. In addition, document the actual dose added to the infusion bag, the duration of the infusion, and the actually delivered dose on the respective IMP administration page in the eCRF.

Refer to Section 7.6 for details on the treatment of overdose.

9.6.2. Pregnancy and Breastfeeding Reporting

If the patient or partner of a patient participating in the study becomes pregnant or in case of breastfeeding, during treatment or within [redacted] after the last dose of IFX-1 or 120 days after the last dose of pembrolizumab treatment, or until [redacted] following discontinuation of study treatment if the patient initiates new anticancer therapy, the investigator should report the pregnancy and breastfeeding exposure to **QLS_IFX1@iqvia.com** via e-mail **within 24 hours** of being notified using the paper based pregnancy/breastfeeding reporting form. In case e-mail contact is not possible, the site can provide the form via FAX line: +353 1 809 9501.

In case of any accompanying Serious Adverse Events the standard reporting procedure via eCRF must be followed (see Section 9.2).

A patient becoming pregnant while on study treatment will immediately be discontinued from treatment and the EOT Visit will be performed.

The patient or partner should be followed by the investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the investigator should notify the sponsor. At the completion of the pregnancy, the investigator will document the outcome of the pregnancy.

9.6.3. Drug-Induced Liver Injury

Potential drug induced liver injury is considered an important medical event. Although it is not always serious by regulatory definition, such event must be handled as SAE.

Wherever possible, timely confirmation within 48 to 72 hours of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential drug induced liver injury event. All occurrences of potential drug induced liver injuries, meeting the defined criteria, must be reported as SAEs.

Potential drug induced liver injury is defined as:

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation ≥3 × upper limit of normal (ULN)

AND

- Total bilirubin ≥2 × ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)

AND

- No cholestatic or other immediately apparent possible causes of AST or ALT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic

9.6.4. Suspected Transmission of an Infectious Agent via Study Drug

For the purposes of reporting, any suspected transmission of an infectious agent (pathogenic or non-pathogenic) via the investigational drug should be considered as an SAE.

A transmission of an infectious agent may be suspected from clinical signs or symptoms, or laboratory findings indicating an infection in a patient exposed to a medicinal product.

In the context of evaluating a suspected transmission of an infectious agent via a medicinal product, care should be taken to discriminate, whenever possible, between the cause (e.g., injection/administration) and the source (e.g., contamination) of the infection and the clinical conditions of the patient at the time of the infection (immuno-suppressed/vaccine).

9.7. Adverse Events of Special Interest

AESIs are events that are considered to have a special meaning or importance for a particular drug or class of drugs. They may be non-serious or serious. Therefore, they should be closely monitored. The site must report all AESIs that occur with start of study treatment, whether considered to be related to study treatment or not, according to Appendix 6. Moreover, AESIs should be documented in the general AE section of the eCRF as well as in the patient file.

9.7.1. IFX-1

This is the first study investigating IFX-1 in a malignant disease. Clinical experience with IFX-1 has been generated in >300 patients with inflammatory diseases, including sepsis and HS.

For this study, the following AEs are defined as AESIs:

- [redacted]

- [redacted]

- [redacted]

9.7.2. Pembrolizumab

For pembrolizumab, AESIs for this study include:

- An overdose of pembrolizumab, as defined in Section 7.6, that is not associated with clinical symptoms or abnormal laboratory results

- An elevated AST or ALT lab value ≥3 × ULN and an elevated total bilirubin lab value ≥2 × ULN and, at the same time, an alkaline phosphatase lab value <2 × ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing

  Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study site guidance for assessment and follow-up of these criteria can be made available. It may also be appropriate to conduct additional evaluation for an underlying etiology in the setting of abnormalities of liver blood tests including AST, ALT, bilirubin, and alkaline phosphatase that do not meet the criteria noted above. In these cases, the decision to proceed with additional evaluation will be made through consultation between the study investigators and the sponsor clinical director. However, abnormalities of liver blood tests that do not meet the criteria noted above are not AESIs for this study.

9.8. Reporting to Competent Authorities and Ethics Committees

The IBs will be the reference document for safety information.

The safety vendor is responsible for submission of suspected unexpected serious adverse reactions (see Appendix 6 I for a definition) to health authorities and Independent Ethic Committees (IEC) in accordance with local regulations.

The investigator is responsible for informing the Independent Review Board (IRB)/IEC in a timely manner and in accordance with local procedures

10. STATISTICAL CONSIDERATIONS

10.1. Sample Size Determination

This study plans to enroll a total of up to approximately 70 patients, including up to 29 patients in Arm A to receive IFX-1 monotherapy and up to 41 patients in Arm B (safety run-in: 9 to 18 patients; Phase II portion: 23 patients) to receive combination therapy with IFX-1 and pembrolizumab.

The 2 treatment arms are evaluated separately. No adjustment for multiplicity will be performed for the application of Simon's 2-stage design in each arm. The sample size of 29 for analyses of the Phase II portion in each treatment arm is based on an optimal Simon's 2-stage design, with 10 patients planned for the first stage and 19 patients planned for the second stage. This sample size is based on a proportion of responders for a drug which is not worth to pursue further of p_0=5%. The proportion of responders of a good drug was set to p_1=20% for this sample size. The null hypothesis that the best ORR $p \leq 0.05$ will be tested versus the alternative hypothesis that $p > 0.05$. This design leads to an expected sample size of about 18 patients per arm and a probability of early termination of 59.9%. If the drug is actually not effective, there is a 4.7% probability of concluding that it is effective (Type I error). If the drug is actually effective, there is a 19.9% probability of concluding that it is not effective (Type II error). After testing the drug on 10 patients in the first stages of both arms, the study will be terminated if no patient responds. If a treatment arm proceeds to the second stage, a total of 29 patients (10 in Stage 1 plus 19 in Stage 2) will be studied for this dose in this treatment arm. If the total number responding is ≤3, the hypothesis of a potentially effective drug is rejected.

10.2. Analysis Sets

For purposes of analysis, the following analysis sets are defined:

Analysis Set	Description
Enrolled Set	All patients who sign the informed consent form
Safety Analysis Set (SAS)	All patients assigned to study treatment and who received ≥1 dose of study treatment (IFX-1 for monotherapy arm, IFX-1 or pembrolizumab for combination arm)
Full Analysis Set (FAS)	All patients assigned to study treatment
Per Protocol Set (PPS)	All patients who received ≥1 dose of study treatment and who have ≥1 post-baseline tumor assessment

Protocol violations will be reviewed in the data review meeting. The decisions will be documented in the meeting minutes and finalized before database lock.

In general, safety analyses will be based on the SAS. The primary efficacy analyses will follow an intention-to-treat concept and will be performed on the FAS.

10.3. Statistical Analyses

The statistical analysis plan (SAP) will be developed and finalized before the first patient is enrolled. The SAP will include the exact definition of endpoints and variables to be analyzed, extensive details on the statistical analysis methods to be used together with the structure of tables and figures to be included as end-of-text tables and figures as well as appended listings for the clinical study report. It will also describe procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

Individual data will be listed. Data will be summarized using suitable descriptive statistics; depending on the structure of the data, summary statistics (e.g., number of observations, mean, standard deviation, minimum, median, maximum, lower quartile, upper quartile) or frequency tables may be used.

All data will be displayed by treatment arm if not specified otherwise.

10.3.1. Efficacy Analyses

All efficacy analyses will be performed on the FAS. All analyses will be conducted separately by treatment arm. The 2 treatment arms will be compared descriptively. Patients will be analyzed descriptively and stratified by locally advanced or metastatic cSCC.

The primary efficacy variable is the best ORR (investigator assessed) based on modified RECIST v1.1 criteria (Eisenhauer et al., 2009) and iRECIST criteria (Seymore et al., 2017). The number and percentage of responders will be displayed per treatment arm along with its 95% confidence interval according to Clopper-Pearson.

Patients who discontinue the study after assignment to treatment due to 1 of the following reasons will be counted as non-responder if they have not shown response before discontinuation:

- Lack of efficacy
- AE at least possibly related to study treatment
- PD/iCPD
- Clinical deterioration

Statistical inference will be based on the thresholds defined by the Simon's 2-stage design. For decision criteria at the interim analysis, please refer to Section 10.3.4. At the final analysis, the null hypothesis of an ORR of ≤5% will be rejected if >3 patients out of a total of 29 patients respond (CR/iCR/PR/iPR). Due to dropouts, the number of patients evaluable for the primary endpoint might not be exactly 29. In this case, appropriate statistical methods will be applied to correct for the deviation from the planned sample size of 29 evaluable patients (Koyama and Chen, 2008). In this case, appropriate statistical methods will be applied to correct for the deviation from the planned sample size of 29 evaluable patients (Koyama and Chen, 2008). Further details will be specified in the SAP.

Additionally, the number and percentage of patients per RECIST tumor response category will be displayed for each scheduled tumor assessment time point.

Secondary Endpoint	**Statistical Analysis Methods**
Response (CR/iCR/PR/iPR) duration	Duration of response will be analyzed for patients who reach at least PR/iPR at any time during the study using Kaplan-Meier methods. A responding patient who experiences any form of progression will be evaluated as a patient with event. The starting point is the first diagnosis of CR/iCR or PR/iPR. The time point of the event will be the diagnosis of progression according to RECIST. Responding patients without progression will be censored at their last tumor assessment showing response. Patients who never responded will be excluded from this analysis.
SD duration	Duration of SD will be analyzed using Kaplan-Meier methods. The starting point is the first study treatment administration. A patient who experiences any form of progression will be evaluated as a patient with event. The time point of the event will be the diagnosis of progression according to RECIST (PD) or iRECIST (iCPD). Patients without progression will be censored at their last tumor assessment showing response or any other best overall response except PD/iCPD.
PFS	PFS will be analyzed using Kaplan-Meier methods. A patient who experiences any form of progression or who

	dies of any cause will be evaluated as a patient with event. The time point of the event will be the diagnosis of the first progression according to RECIST/iRECIST or the date of death. Patients without progression and still alive will be censored at their last tumor assessment.
OS	OS will be analyzed using Kaplan-Meier methods. Death by any cause will be evaluated as event. Patients who are still alive when they discontinue the study will be censored at their last recorded date of being alive.
Disease control rate	The number and percentage of patients with SD/confirmed SD (iSD) per modified RECIST v1.1/iRECIST or PR/iPR or CR/iCR will be displayed per tumor assessment timepoint.

Exploratory endpoints will be analyzed descriptively. Further details will be provided in the SAP.

10.3.2. Safety Analyses

All safety analyses will be performed on the SAS.

An AE is considered as treatment emergent if it starts during or after first administration of study treatment (IFX-1 or pembrolizumab). The number and percentage of patients with TEAEs, SAEs, and AESIs for IFX-1 and/or pembrolizumab will be analyzed, as well as the number of TEAEs, SAEs, and AESIs with the respective MedDRA System Organ Class and Preferred Term. Where AEs are grouped by NCI CTCAE grade or relationship, the maximum grade/relationship per patient and class of AE will be considered. The described analyses will be performed for the treatment period and the follow-up period separately. AEs reported during screening or before first study treatment administration will be categorized as pre-treatment AEs.

Safety laboratory, vital signs, and 12-lead ECG parameters will be analyzed by summary statistics (e.g., number of observations, mean, standard deviation, minimum, median, maximum, lower quartile, upper quartile) for absolute values and changes from baseline by visit. Shift tables comparing baseline and the worst post-baseline assessment will be prepared if applicable.

Categorical safety parameters, like findings from physical examination, will be summarized by absolute and relative frequencies by time point.

10.3.3. Exploratory Analyses

PK, pharmacodynamics, and biomarker exploratory analyses will be described in the SAP finalized before database lock.

10.3.3.1. Pharmacokinetic Analyses

Actual PK sampling date and times will be documented and the plasma concentration of IFX-1 will be assessed by time point. Summary statistics will be provided for the PK concentrations of

IFX-1 at all measured time points including also the geometric mean and its coefficient of variation. PK parameters including but not limited to C_{max} and C_{trough}, will be analyzed using descriptive statistics including also the geometric mean and its coefficient of variation.

10.3.3.2. Immunogenicity Analyses

The number and percentage of patients with detectable ADAs against IFX-1 will be displayed per time point and overall post-baseline.

10.3.3.3. Quality of Life Analyses

QoL will be assessed by the EORTC-QLQ-C30. The change from baseline of the total score will be analyzed descriptively at each measured time point as a secondary endpoint.

10.3.3.4. Pharmacodynamic Analyses

Pharmacodynamics endpoints will be analyzed using descriptive statistics.

10.3.4. Interim Analyses

10.3.4.1. Formal Interim Analysis Based on Simon's 2-Stage Design

An interim analysis based on Simon's 2-stage design (Simon, 1989) of treatment response will be performed after Stage 1 in both treatment arms (monotherapy Arm A and combination therapy Arm B) before enrollment into Stage 2.

The interim analysis will be performed on the first 10 patients evaluable for the Phase II portion per arm when these 10 patients have performed their third post-baseline tumor assessment OR discontinued treatment. At the time of the interim analysis, a treatment arm will be discontinued if 0 responders are observed in the respective treatment arm. A responder is defined as in Section 10.3.1. Each treatment arm will be evaluated separately such that it may occur that enrollment into both arms is stopped, enrollment into 1 arm is stopped and the other is continued to the second stage, or enrollment into both arms is continued. If both arms are discontinued after Stage 1, the final analysis will be performed after all patients enrolled in Stage 1 will have completed or discontinued the study and described in a clinical study report. If enrollment is stopped, patients will still receive treatment until disease progression (EOT), or are discontinued due to other reasons, and will then be followed up for 12 months.

10.3.4.2. Safety Run-In Based on 3+3 Design (Combination Therapy Arm B)

The safety run-in phase in the combination Arm B will follow a 3+3 design for escalation of the IFX-1 treatment regimen based on the following escalation rules:

- If 0 of 3 patients experience a DLT during the DLT observation period (see Section 7.2.2.2.3) at a certain IFX-1 treatment regimen, the subsequent 3 patients will be enrolled in the next higher IFX-1 treatment regimen.

- If 1 of 3 patients experience a DLT, another 3 patients will be enrolled at the same IFX-1 treatment regimen.
  - If 1 of 6 patients (i.e., none of the subsequent 3 patients) experiences a DLT, the combination arm will escalate to the next IFX-1 treatment regimen.
  - If >1 of 6 patients at the same IFX-1 treatment regimen experience a DLT, this treatment regimen will be stopped.
- If >1 of 3 patients at the same IFX-1 treatment regimen experience a DLT, this treatment regimen will be stopped.
- If a treatment regimen is stopped, the next lower treatment regimen is considered as MTD.
- In the highest IFX-1 treatment regimen (regimen 3): if ≤1 of 6 patients experience a DLT, this will be determined as RP2D.
- 6 patients will need to be treated at the MTD or at the highest IFX-1 dose level (Regimen 3, if MTD was not reached) to decide if this dose can be selected as RP2D which will then be explored in the Phase II portion of Arm B. In case only 3 patients will have been previously treated at the MTD or highest IFX-1 dose level, 3 more patients will be added to this cohort. If 6 patients were already treated at the proposed dose level, then additional patients will not be required and the decision on the RP2D will be made based on the available data.
- The subsequent patients will be enrolled at the RP2D to fill up the first stage of the Simon's 2-stage design for the combination arm (4 additional patients to reach the required sample size of 10).

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12. APPENDICES

Appendix 1 Visit Procedures

Screening Visit

- Informed consent procedures
- Check of all inclusion and exclusion criteria
- Biopsy for confirmation of diagnosis of cSCC for locally advanced cSCC patients if no archival tumor tissue is available
- Document demography, medical and disease history (including hepatitis), prior medication
- Disease/response assessment
- QoL assessment
- Documentation of concomitant disease and concomitant medication
- Safety assessments:
  - Height, weight
  - Physical examination, ECOG PS
  - Vital signs
  - AEs
  - ECG
- Blood and urine samples for complete safety laboratory
- Pregnancy testing (WOCBP only): serum beta-HCG test within 72 hours before first drug administration
- Tissue sampling for biomarker assessments (skin, metastasis)

Treatment Visits

The Treatment Period will comprise mainly weekly visits until Cycle 1 Days 22 followed by bi-weekly visits until the EOT. Visits will have an accepted time window of between 1 and ±3 days as specified in the SoA (Table 1).

The following assessments and procedures will be performed during the treatment period:

- Re-check of all inclusion and exclusion criteria (Cycle 1 Day 1 pre-dose)
- Disease/response assessment (Day 1 of each cycle from Cycle 2 on until EOT Visit)
- QoL assessment (Cycle 1 Day 1 pre-dose-; Day 1 of each cycle from Cycle 2 on until EOT Visit)
- Documentation of concomitant disease and concomitant medication (Cycle 1 Days 1 [pre-dose], 4, 8, 15, 22, and 36; Days 1, 15, and 29 of each cycle from Cycle 2 on until EOT Visit)

- Check of re-dosing criteria pre-dose at Cycle 1 Days 4, 8, 15, 22, and 36, and Days 1, 15, and 29 of each cycle from Cycle 2 on until EOT Visit
- Study treatment administration by intravenous route as 30-minute (-5/+10 minutes) infusion:
  - Arm A (IFX-1 monotherapy):
    - Cycle 1 Days 1, 4, 8, and 15: **800** mg IFX-1
    - Cycle 1 Day 22 and Day 36, and from Cycle 2 onwards until EOT (Days 1, 15, 29 of each cycle): **1600** mg IFX-1 Q2W
  - Arm B – combination regimen 1:
    - Cycle 1 Days 1, 4, 8, and 15: **400** mg IFX-1 + 400 mg pembrolizumab on Day 8
    - Cycle 1 Day 22 and Day 36, and from Cycle 2 onwards until EOT (Days 1, 15, 29 of each cycle): **800** mg IFX-1 Q2W + 400 mg pembrolizumab Q6W (on Day 1 of each cycle)
  - Arm B – combination Regimen 2:
    - Cycle 1 Days 1, 4, 8, and 15: **600** mg IFX-1 + 400 mg pembrolizumab on Day 8
    - Cycle 1 Day 22 and Day 36, and from Cycle 2 onwards until EOT (Days 1, 15, 29 of each cycle): **1200** mg IFX-1 Q2W + 400 mg pembrolizumab Q6W (on Day 1 of each cycle)
  - Arm B – combination regimen 3:
    - Cycle 1 Days 1, 4, 8, and 15: **800** mg IFX-1 + 400 mg pembrolizumab on Day 8
    - Cycle 1 Day 22 and Day 36, and from Cycle 2 onwards until EOT (Days 1, 15, 29 of each cycle): **1600** mg IFX-1 Q2W + 400 mg pembrolizumab Q6W (on Day 1 of each cycle)
- Safety assessments:
  - Weight (Cycle 1 Days 1 [pre-dose], 4, 8, 15, 22, and 36; Days 1, 15, and 29 of each cycle from Cycle 2 on until EOT Visit)
  - Physical examination (Cycle 1 Days 1 [pre-dose], 4, 8, 15, 22 and36; Days 1, 15, and 29 of each cycle from Cycle 2 on until EOT Visit)
  - Vital signs (Cycle 1 Days 1 [pre- and post-dose], 4, 8, 15, 22 and 36; Days 1, 15, and 29 of each cycle from Cycle 2 on until EOT Visit)
  - AEs (Cycle 1 Days 1 [pre- and post-dose], 4, 8, 15, 22 and 36; Days 1, 15, and 29 of each cycle from Cycle 2 on until EOT Visit)
  - ECG (Cycle 1 Day 1 [pre- and post-dose], Cycle 2 Day 1 [post-dose])
- Blood and urine samples for safety laboratory:
  - Hematology (Cycle 1 Days 1 [pre-dose], 8, 15, 22, and 36; Cycle 2 Days 1, 15, and 29; and Day 1 of each subsequent cycle onwards until EOT Visit)

  - Biochemistry (Cycle 1 Days 1 [pre-dose], 8, 15, 22, and 36; Cycle 2 Days 1, 15, and 29; and Day 1 of each subsequent cycle onwards until EOT Visit)
  - Coagulation parameters (Cycle 1 Day 1 [pre-dose], Cycle 2 Day 1)
  - Urinalysis (Cycle 1 Days 1 [pre-dose], 8, 15, 22, and 36; Cycle 2 Days 1, 15, and 29; and Day 1 of each subsequent cycle onwards until EOT Visit)
  - Thyroid stimulating hormone, preferably total T3, free T4 (or other T3/T4 fractions depending on local standards) (Cycle 1 Day 8, and Day 1 of each subsequent cycle until EOT Visit)
  - Urine pregnancy test (WOCBP) (Cycle 1 Days 8, 22, and 36; Days 1, 15, and 29 in Cycle 2 and each subsequent cycle until EOT Visit)
- Plasma and serum sampling pre-dose:
  - C3a at Cycle 1 Day 1 [pre-dose]
  - C5a in plasma (Cycle 1 Days 1 [pre-dose], 8, 15, 36 and 22; Day 1 of Cycles 2, 3, 5, and then of every other cycle until EOT Visit)
  - ADAs against IFX-1 in serum (Cycle 1 Days 1 [pre-dose] 15, 22 and 36; Day 1 of Cycles 2, 3, 5, and then of every other cycle until EOT Visit)
- PK parameter assessment:
  - At pre-dose on Cycle 1 Days 1, 8, 15, 22, and 36; Day 1 of Cycles 2, 3, 5, and then of every other cycle until EOT Visit
  - Additionally, post dose H0+0.5h (-5/+10 minutes, but not before the end of IFX-1 administration), or just after the end of administration in case of decrease in infusion rate on Cycle 1 Days 1 and 22
- Tumor biomarkers
  - Skin biopsy (Screening, and for Stage 2 patients only: Cycle 2 Day 1 (mandatory), once at time of CR/iCR/PR/iPR (optional), and/or at PD (optional)
  - If skin biopsy is not possible: Metastasis biopsy (Screening, and for Stage 2 patients only: Cycle 2 Day 1, once at time of CR/iCR/PR/iPR, and/or at PD (optional)

End of Treatment Visit

- Disease/response assessments
- QoL
- Documentation of concomitant disease and concomitant medication
- Safety assessments:
  - Weight
  - Physical examination, ECOG PS
  - Vital signs

  - AEs
  - ECG
- Safety laboratory (hematology, biochemistry, coagulation parameters, urinalysis, thyroid stimulating hormone, preferably total T3, free T4 (or other T3/T4 fractions depending on local standards), urine pregnancy test [WOCBP])
- Sampling for PK, C5a, immunogenicity of IFX-1(ADA)
- Only Stage 2 patients: Skin and metastasis biopsy (optional)

Follow-Up Visits (every 12 weeks [±7d]) and End of Study Visit (=last follow-up)

- Disease/response assessment (only if discontinuation of IFX-1 treatment for other reasons than PD/iCPD)
- QoL
- Documentation of:
  - AEs
  - Survival status
  - Further antineoplastic therapies
- Urine pregnancy test (WOCBP): on the first FU Visit for Arm A, on the first FU visit and 120 days after the last dose of pembrolizumab for Arm B.
- Only at first FU Visit: Sampling for PK, C5a
- ADAs against IFX1 (only at first FU Visit)

Appendix 2 Clinical Laboratory Tests

Protocol-required laboratory assessments are detailed in Table 2, specific requirements for in- or exclusion in Section 6.1 and Section 6.2. Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 2 Protocol-Required Safety Laboratory Assessments

Assessment	Parameters	
Hematology	Hemoglobin Hematocrit Platelet count Red blood cell count Red blood cells (MCV)	White blood cell count with differentials (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Coagulation parameters	aPTT	PT
Clinical chemistry [a]	ALT (SGPT) AST (SGOT) ALP LDH Total bilirubin Total protein Albumin Amylase Lipase	Urea Uric acid Sodium Potassium Calcium Magnesium Creatinine Glucose CRP
Urinalysis (Dipstick)[b]	PH Glucose Leucocytes Protein Blood	
Other screening tests	TSH, Total T3, Free T4 (or other T3/T4 fractions depending on local standard) FSH and estradiol (as needed in women of non-childbearing potential only) Serum or urine hCG pregnancy test (as needed in women of childbearing potential)	

ALP=alkaline phosphatase; ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); aPTT=activated partial thromboplastin time; AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); CRP=C reactive protein; FSH=follicle stimulating hormone; hCG=human chorionic gonadotropin; LDH=lactate dehydrogenase; MCV=mean corpuscular volume; PT=prothrombin time; TSH=thyroid stimulating hormone.

a Details of liver chemistry stopping criteria, required actions, and follow up assessments are given in Section 9.6.3. All events of ALT ≥3 × ULN and bilirubin ≥2 × ULN (35% direct bilirubin) or ALT ≥3 ULN and INR >1.5 (if measured), may indicate severe liver injury (possible Hy's Law) and must be reported as an SAE.

b Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

Investigators must document their review of each laboratory safety report.

Appendix 3 RECIST

RESPONSE EVALUATION CRITERIA IN SOLID TUMORS: RECIST GUIDELINE (VERSION 1.1)

Response and progression will be evaluated in this study using the international criteria proposed by the revised RECIST v1.1 guideline (Eisenhauer et al., 2009) and according to iRECIST (Seymore et al., 2017; see Appendix 4), which introduces additional tumor assessments and evaluation criteria in situations where pseudo-progression is suspected.

Changes in the largest diameter (uni-dimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

Selection of Lesions

- **Measurable disease:** Measurable lesions are defined as those that can be accurately measured in ≥1 dimension (longest diameter to be recorded) as ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).
- **Malignant lymph nodes:** To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be ≤5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.
- **Non-measurable disease:** All other lesions (or sites of disease), including small lesions (longest diameter <10 mm [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable. Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. “Cystic lesions” thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non cystic lesions are present in the same patient, these are preferred for selection as target lesions.
- **Target lesions:** All measurable lesions ≤2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum

diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

- **Non-target lesions:** All other lesions (or sites of disease) including all measurable lesions not selected as one of the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

Methods for Assessment of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never >4 weeks before the beginning of the treatment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

- **Clinical lesions**: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm (≥1 cm) diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by standardized medical color photography, including a ruler to estimate the size of the lesion, is recommended.
- **Chest x-ray**: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- **Conventional CT and MRI:** This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness >5 mm (0.5 cm), the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situation.
- **Positron emission tomography (PET)-CT**: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with intravenous and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.
- **Ultrasound**: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from 1 assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

- **Endoscopy, laparoscopy**: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in studies where recurrence following CR or surgical resection is an endpoint.
- **Tumor markers**. Tumor markers alone cannot be used to assess response. If markers are initially above the ULN, they must normalize for a patient to be considered in complete clinical response.
- **Cytology, histology**: These techniques can be used to differentiate between PR and CR in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or SD is mandatory to differentiate between response or SD (an effusion may be a side effect of the treatment) and PD.
- **Fluorodeoxyglucose (FDG)-PET**. While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible "new" disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
  - Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
  - No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDGPET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
  - FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

    Note: A "positive" FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

Response Criteria

Evaluation of Target Lesions

- **CR:** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).
- **PR**: ≥30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters

- **PD:** ≥20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of ≥5 mm (0.5 cm).

  Note: The appearance of ≥1 new lesion is also considered progression.

- **SD:** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

Evaluation of Non-Target Lesions

- **CR:** Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).

  Note: If tumor markers are initially above the ULN, they must normalize for a patient to be considered in complete clinical response.

- **Non-CR/Non-PD:** Persistence of ≥1 non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

- **PD:** Appearance of ≥1 new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase. Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or principal investigator).

Evaluation of Response

The best overall response is the best response recorded from the start of the treatment until PD/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). The patient's best overall response assignment will depend on the achievement of both measurement and confirmation criteria over the several tumor response assessment time points. Revised RECIST v1.1 (Eisenhauer et al., 2009) criteria for response evaluation at a specific tumor assessment are summarized in the table:

Response Assignment According to Revised Response Evaluation Criteria in Solid Tumors (Version 1.1)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response When Confirmation is Required[a]
CR	CR	No	CR	>4 weeks confirmation
CR	Non-CR/Non-PD	No	PR	>4 weeks confirmation
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once >4 weeks from baseline
PD	Any	Yes or No	PD	No prior SD, PR, or CR
Any	PD	Yes or No	PD	
Any	Any	Yes	PD	

CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease.

a In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as PD.

COMPOSITE RESPONSE CRITERIA FOR PATIENTS WITH LOCALLY ADVANCED cSCC

This appendix describes clinical response criteria for externally visible lesions that can be measured bi-dimensionally using digital medical photography. This appendix also provides composite response criteria for disease that is measurable by both clinical response criteria and RECIST v1.1.

Radiologic imaging (preferably, MRI with gadolinium) will be essential in the evaluation of tumors that have subdermal components that cannot be adequately assessed by digital medical photography.

Response assessments occur after every cycle. Standardized digital photographs of the externally visible component of all target lesions must be obtained at baseline and at the time of each subsequent tumor assessment. Guidelines for digital medical photography will be provided to the sites. Investigators will also provide a clinical description of the externally visible target lesion(s) at baseline and at each tumor assessment, as well as comments on any changes in the lesion(s) since the previous assessment.

SPECIAL ISSUES FOR EXTERNALLY VISIBLE TUMORS:

1) Anatomic Defects

Regarding tumor around a surgical cavity/anatomic defect (e.g., rhinectomy), such lesions should be considered non-measurable unless there is a nodular lesion measuring ≥10 mm in maximal bi-dimensional perpendicular diameters. The surgical cavity or anatomic defect should not be considered in measuring the lesion.

2) Indeterminate-Appearing Tissue

If there is uncertainty about whether a given lesion or area of a lesion represents malignancy versus benign process (e.g., scarring, fibrosis), biopsies should be obtained at any tumor assessment time point. Indeterminate-appearing areas (e.g., scarring, fibrosis) are included in the tumor measurements unless biopsies are obtained to establish benign status. To reduce risk of sample error, biopsy of only a single area on the tumor is not allowed. Biopsy of ≥2 separate areas of the lesion are required when biopsy is indicated. Each biopsy will be performed in a pairwise manner (approximately adjacent) so that there will be 1 sample for local review and 1 for optional central review for each biopsy. As such, when the decision is made to perform biopsy, ≥4 biopsy samples are obtained (biopsy of 2 separate areas, with 2 biopsies in each area: 1 for central, 1 for local from each area). Biopsy samples will not be bisected or split in half for local and central review; rather, separate adjacent samples will be obtained. Further details will be given in the Biopsy Handling Manual.

Note on Timeline for Finalization of Measurement/Response Assessment: Generally, baseline disease measurements and response evaluation should be completed on the day of the visit at which digital medical photography was performed. However, for visits in which tumor biopsies are performed, it is understood that the local pathology report may not be available for up to 5 business days after the biopsy.

When biopsies are performed to distinguish between benign versus malignant tissue, the annotated photograph for that visit should clearly indicate the region of the tumor that was biopsied to distinguish benign versus malignant tissue. Within 1 week of the date of biopsies, the investigator should finalize the tumor measurements for that visit with the benefit of the local pathology report. For circumstances in which the intent of the biopsy is to distinguish between disease stability and response, it is not necessary to hold study treatment while the local pathology report is pending.

For circumstances in which the biopsy, if positive, would result in discontinuation of study treatment due to progression, treatment should be held until biopsy results are finalized and progression has been ruled out.

3) Local Versus Central Review

An independent photographic review committee, with access to de-identified digital medical photography results and biopsy results, may be installed by the sponsor upon emerging results. As such, independent photographic reviews will not be "real-time". Clinical management decisions generally will be as per investigator response assessments and local pathology review. In case an independent photographic review committee will be installed during ongoing treatment of patients in the study, and in the unlikely event that independent review yields major differences with the local response assessment that could have implications for the ongoing management of an active patient on study, the situation will be discussed between the sponsor and the investigator in order to determine patient management.

4) Confirmation of Responses

After any observation of an objective response (i.e., CR/iCR, PR/iPR), confirmatory digital standardized medical photography (and radiologic imaging, if performed as part of the initial response assessment) will be obtained ≥4 weeks following initial documentation of objective response. For any complete responses observed in digital medical photography of externally visible target lesions, confirmatory biopsies are required to establish status of CR/iCR.

5) Metastatic cSCC Patients with Externally Visible Tumors

Externally visible tumors will generally be followed by RECIST v1.1 and iRECIST criteria. It is possible that some patients with metastatic cSCC may also have externally visible lesions that are measurable by digital medical photography. In such circumstances, the externally visible lesions generally will be followed as nontarget lesions. The exception to this rule would be a patient with externally visible lesions in whom the only M1 lesions are not measurable by RECIST (e.g., a patient with bone-only metastases), in which case the externally visible lesions (lesion size ≥10 mm in baseline dimensional perpendicular axes) would be target lesions and followed as per clinical response criteria in this appendix, and the -non-measurable metastatic lesions (e.g., bone metastases) would be followed as non-target lesions. For any target lesions that are measured by digital medical photography, measurements will be bi-dimensional.

6) Patients with Deeply Invasive Tumors

Tumor measurements for these patients will generally be performed with digital medical photography (bi-dimensional measurements). However, some patients may have deeply invasive target lesions in which tumor measurements can better be obtained with cross-sectional imaging (e.g., MRI with gadolinium or CT with contrast). For any target lesions that are measured by cross-sectional imaging (MRI gadolinium or CT with contrast), measurements will uni-dimensional according to RECIST v1.1.

Clinical Response Criteria for Externally Visible Tumors (for patients with locally advanced cSCC, and patients with metastatic cSCC in which target lesions are followed by digital medical photography)

A. Externally Visible Tumor Dimension

The externally visible component of target lesion(s) will be measured using bi-dimensional World Health Organization (WHO) criteria as the sum of the products (of individual target lesions) in the longest dimension and perpendicular second longest dimension at each tumor assessment and will be documented as described in a separate manual. In the absence of substantial change in lesion geometry, subsequent visit measurements should be performed in the same axes and the investigator should refer to the previous visit's annotated photographs as a starting point to identify axis for measurement when making subsequent assessments.

Clinical response criteria for externally visible tumor(s) require bi-dimensional measurements according to WHO criteria, and are as follows:

- **CR of externally visible disease**: All target lesion(s) and non-target lesion(s) no longer visible, maintained for ≥4 weeks. Documentation of CR requires confirmation by biopsies of site(s) of externally visible target lesion(s) with histologic confirmation of no residual malignancy, per central pathology review, as described in a separate manual. In the absence of such histologic confirmation, a patient cannot be deemed to have experienced CR and the best response would be PR.
- **PR of externally visible disease**: Decrease of 50% (WHO criteria) or greater in the sum the products of perpendicular longest dimensions of target lesion(s), maintained for ≥4 weeks
- **Progression of visible disease**: Increase of ≥25% (WHO criteria) in the sum of the products of perpendicular longest dimensions of target lesion(s). In rare cases, unequivocal progression of a non-target lesion may be accepted as PD.
- **Stable externally visible disease**: Not meeting criteria described above for CR or PR or SD of externally visible disease

B. New Lesions

A new cutaneous lesion consistent with cSCC will be considered as clinical PD if the lesion is ≥10 mm in both maximal perpendicular diameters and can be clearly documented as not being previously present, unless it is confirmed on biopsy not to be consistent with cSCC. If a new cutaneous lesion is not biopsied or if the histology is inconclusive, it should be considered cSCC and deemed clinical PD.

Overall Clinical Responses for Locally Advanced cSCC Lesions That are Measured by Digital Medical Photography

Externally Visible Tumor Dimension[a]	**New Lesions**[a]	**Clinical Response**
CR of externally visible disease	No	Clinical CR[b]
PR of externally visible disease	No	Clinical PR
SD of externally visible disease	No	Clinical SD
PD of externally visible disease	Yes or No	Clinical PD
Any	Yes	Clinical PD

CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease

a See above for definitions.

b Negative biopsy showing no residual malignant cells is required for any lesion be deemed clinical CR.

Composite Response Criteria

These criteria are for patients who have locally advanced or metastatic cSCC that is measurable by BOTH clinical response criteria by digital medical photography and RECIST v1.1 using radiologic imaging.

The "Clinical Response" column in this table will be based on the results of the "Clinical Response" (far-right) column of the table above.

Clinical Response (Digital Medical Photography)	RECIST v1.1 Response (Radiology)	Composite (Overall): Clinical + RECIST Response
clinical CR	CR or NA	CR
NA	CR	CR
clinical CR	PR or SD	PR
clinical PR	CR, PR, or SD, or NA	PR
NA	PR	PR
clinical SD	CR or PR	PR
clinical SD	SD or NA	SD
NA	SD	SD
clinical PD	Any	PD
Any	PD	PD

CR=complete response; NA="not applicable" (e.g., assessment not done); PD=progressive disease; PR=partial response; SD=stable disease.

In addition, if all previously inoperable target lesions are rendered operable with clear margins obtained at the time of surgery, this will be considered a PR. If the investigator deems a previously unresectable lesion to be potentially resectable, due to response to study treatment, the medical monitor should be consulted prior to any surgical procedure being performed. A decision will be rendered by the sponsor as to whether the planned surgical intervention is compatible with study requirements. (This statement does not apply to patients in emergency life-threatening situations that require immediate surgery).

Note: If composite (overall) response evaluation of PD emerges for the first time, iRECIST assessment criteria for new lesion documentation apply (see Appendix 4) and the investigator will assess the clinical status of the patient in case pseudo-progression is suspected.

C. Ulcerated Lesions

This section only pertains to target lesions that have extensive ulceration at baseline that prevents measurement by the above methods in this appendix. Response criteria are as follows:

- **CR**: Re-epithelialization of the entire baseline area of ulceration of target lesion(s), maintained over ≥4 weeks
- **PR**: There are no criteria for partial response.

- **SD:** Not meeting criteria for CR or PD
- **PD:** New ulceration of target lesion(s) not related to (i.e., in a location separate from) tissue biopsy or other known trauma, persistent without evidence of healing for ≥2 weeks

Response and progression will be evaluated in this study using the international criteria proposed by the revised RECIST v1.1 guideline (Eisenhauer et al., 2009) and according to iRECIST (Seymore et al., 2017; see Appendix 4), which introduces additional tumor assessments and evaluation criteria in situations where pseudo-progression is suspected.

Appendix 4 iRECIST

Response and progression will be evaluated in this study using the international criteria proposed by the revised RECIST v1.1 guideline (Eisenhauer et al., 2009) and according to iRECIST (Seymore et al., 2017), which introduces additional tumor assessments and evaluation criteria in situations where pseudo-progression is suspected.

This appendix describes the iRECIST process for assessment and evaluation of disease progression.

Tumor Assessment at Screening and Prior to iRECIST Progression

At every tumor assessment, target and non-target lesions identified at baseline by RECIST v1.1 will be assessed according RECIST v1.1. Until first radiographically assessed disease progression based on RECIST v1.1, there is no distinct iRECIST assessment. Accordingly, possible response evaluation outcomes are CR, PR, SD, PD, and not evaluable.

Response Evaluation and Decision at RECIST v1.1 Progression

At first radiographic assessment of disease progression according to RECIST v1.1, new lesions will be classified as measurable or non-measurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST v1.1. From measurable new lesions, ≤5 lesions total (≤2 per organ), may be selected as New Lesions – Target. The sum of diameters of these lesions will be calculated and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – Non-target.

For patients whose radiological tumor assessment show evidence of disease progression by RECIST v1.1 criteria, the investigator will decide whether to continue a patient on study treatment and repeat imaging according to iRECIST or discontinue the patient according to disease progression according to RECIST v1.1. This decision by the investigator should be based on the patient's overall clinical condition, in particular in the assessment of clinical stability.

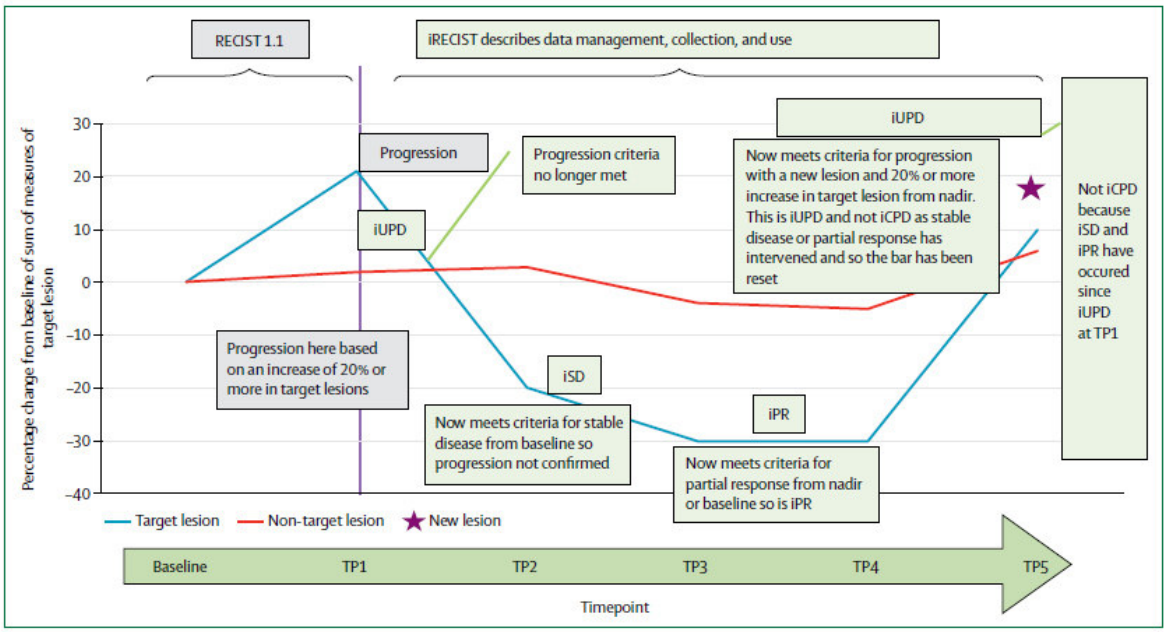
Clinical stability is defined as the following:

- No decline in ECOG PS
- Absence of increases of clinically relevant disease-related symptoms and signs assessed to be associated with disease progression
- No requirements for intensified management of disease-related symptoms, including increased analgesia, radiation, or other palliative care

Any patient deemed **clinically unstable** should be discontinued from study treatment at site-assessed first radiologic evidence of disease progression and assigned a response evaluation of PD (according to RECIST v1.1), and it is not required to have repeat tumor imaging for confirmation of PD by iRECIST (iCPD).

If the patient is deemed to be clinically stable, and the investigator decides to continue treatment, new response categories defined by iRECIST, including iUPD and iCPD, will be used from there on (using iRECIST for patient management as shown in the figure below).

RECIST v1.1 and iRECIST: An Example of Assessment



iCR=complete response; iCPD=confirmed progression; iPR=partial response; iSD=stable disease; iUPD=unconfirmed progression; RECIST=Response Evaluation Criteria in Solid Tumors; TP=timepoint.
Note: Prefix "i" indicates immune responses assigned using iRECIST; others without "i" are confirmed by RECIST v1.1.
Source: Seymore et al., 2017

Additional imaging for confirmation should be scheduled 4 to 8 weeks from the imaging on which iUPD is seen. This may correspond to the next visit in the original visit schedule. Images should continue to be sent to the central imaging vendor for potential retrospective independent response evaluation

Response Evaluation After the First iUPD

The response evaluation of the subsequent confirmation imaging proceeds at scheduled visits, as before, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR, see table below.

Example Scenarios of Assignments of Best Overall Response using iRECIST After First Diagnosis of iUPD

	Timepoint response n	**Timepoint response n+1**	**Timepoint response n+2**	**Timepoint response n+3**	**Timepoint response n+4**	**iBOR**
Example 1	iUPD	iPR, iSD, or NE	iCR	iCR	Any	iCR
Example 2	iUPD	iPR	iPR	Any except iCR	Any except iCR	iPR
Example 3	iUPD	iUPD, iSD or NE	iPR	iPR	Any except iCR	iPR
Example 4	iUPD	iSD	Any, except iPR, iCR	Any, except iPR, iCR	Any, except iPR, iCR	iSD
Example 5	iUPD	Any (no iCPD)	iUPD	iCPD	NA	iCPD
Example 6	iUPD	iUPD (no iCPD)	iCPD	NA	NA	iCPD
Example 7	iUPD	iCPD	NA	NA	NA	iCPD

iBOR=best overall response; iCR=complete response; iCPD=confirmed progression; iPR=partial response; iSD=stable disease; iUPD=unconfirmed progression; NA=not applicable; NE=not evaluable; RECIST=Response Evaluation Criteria in Solid Tumors.
Note: Prefix "i" indicates immune responses assigned using iRECIST; others without "i" are confirmed by RECIST v1.1.
Adapted from Seymore et al., 2017

If progression is confirmed, the overall response will be iCPD. iCPD is present if any of the factors that were the basis for the initial iUPD show worsening, e.g., ANY of the following occurs:

- For target lesions, worsening is a further increase in the sum of diameters of ≥5 mm, compared to any prior iUPD time point.
- For non-target lesions, worsening is any relevant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the "unequivocal" standard of RECIST v1.1.
- For new lesions, worsening is any of these:
  - An increase in the new lesion sum of diameters by ≥5 mm from a prior iUPD time point
  - Visible growth of new non-target lesions
  - The appearance of additional new lesions
  - Any new factor appears that would have triggered PD by RECIST v1.1

NOTE: If a patient has iCPD as defined above, but is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered following consultation with the sponsor. In this case, if study treatment is continued, tumor imaging should continue following the intervals as outlined in the SoA (Table 1) and submitted to the central imaging vendor.

Persistent iUPD

If progression is not confirmed, the overall response remains iUPD. iUPD is present if:

- None of the progression-confirming factors identified above occurs AND

- The target lesion sum of diameters (initial target lesions) remains above the initial PD threshold (by RECIST v1.1).

Resolution of iUPD

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR, if:

- None of the progression-confirming factors identified above occurs, AND
- The target lesion sum of diameters (initial target lesions) is not above the initial PD threshold.

The response is classified as iSD or iPR (depending on the sum of diameters of the target lesions), or iCR if all lesions resolve.

In this case (iSD, iPR, or iCR could be assigned), the initial iUPD is considered to be pseudo progression, and the level of suspicion for progression is 'reset'. This means that the next visit that shows radiographic progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD- can be assigned.

Detection of Progression at Visits After Pseudo-progression Resolves

After resolution of pseudo-progression (i.e., achievement of iSD/iPR/iCR), iUPD is indicated by any of the following events:

- Target lesions
  - Sum of diameters reaches the PD threshold (≥20% and ≥5 mm increase from nadir) either for the first time, or after resolution of previous pseudo-progression. The nadir is always the smallest sum of diameters seen during the entire study, either before or after an instance of pseudo-progression.
- Non-target lesions
  - If non-target lesions have never shown unequivocal progression, their doing so for the first-time results in iUPD.
  - If non-target lesions have shown previous unequivocal progression, and this progression has not resolved, iUPD results from any relevant further growth of non-target lesions, taken as a whole.
- New lesions
  - New lesions appear for the first time
  - Additional new lesions appear
  - Previously identified new target lesions show an increase of ≥5 mm in the new lesion sum of diameters, from the nadir value of that sum.
  - Previously identified non-target lesions show any relevant growth.

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see *Response Evaluation After the First iUPD*, described above) is repeated. Progression must be confirmed before iCPD can occur.

The decision process is identical to the iUPD confirmation process for the initial PD, with 1 exception: If new lesions occurred at a prior instance of iUPD, and at the confirmatory imaging the burden of new lesions has increased from its smallest value (for new target lesions, the sum of diameters is ≥5 mm increased from its nadir), then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR, or until a confirmatory factor causes iCPD.

Additional details about iRECIST are provided in the iRECIST publication (Seymore et al., 2017).

Appendix 5 Regulatory and Ethical Considerations

I. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, informed consent form (ICF), IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.

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 in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other relevant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

II. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

III. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorized representative and answer all questions regarding the study.

Patients must be informed that their participation is voluntary. Patients 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 requirements, where applicable, and the IRB/IEC or study site.

The medical record must include a statement that written informed consent was obtained before the patient 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.

Patients must re-consent to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the patient or the patient's legally authorized representative.

A patient who is rescreened is not required to sign another ICF if the rescreening occurs within the originally planned screening window before drug administration.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each patient the objectives of the exploratory research. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a patient's agreement to allow any remaining specimens to be used for exploratory research. Patients who decline to participate in this optional research will not provide this separate signature.

IV. Data Protection

Patients will be assigned a unique identifier by the sponsor. Any patient records or datasets that are transferred to the sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.

The patient must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The sponsor will ensure that all safeguards are in place to minimize any eventual risk of breaches and complies otherwise with the requirements of European Union General Data Protection Regulation (GDPR Regulation (EU) 2016/679). The sponsor will regularly check all procedures

relevant to the processing of personal data, as to ensure privacy by design and compliance with this regulation.

V. Administrative and Committees Structure

Detailed information will be provided in the Steering Committee Charter.

VI. Publication Policy

The results of this study may be published or presented at scientific meetings. Individual publications are allowed only after publication of the entire study. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with 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 mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

In accordance with consistent editorial practice, the sponsor supports publication of multicenter studies in their entirety and not as individual center data unless as ancillary study/data.

All publications in peer-reviewed medical journals resulting from this study will be listed in the original study protocol registration record (e.g., on ClinicalTrials.gov).

VII. Dissemination of Clinical Study Information

The sponsor will provide the relevant study protocol information in a public database (e.g., ClinicalTrials.gov, https://clinicaltrials.gov/) before or at commencement of the study. The sponsor may also provide study information for inclusion in national registries according to local regulatory requirements.

If a potential patient contacts the sponsor regarding participation in the study, the investigator agrees that the sponsor may forward the study site and contact details to the patient. Based on the inclusion and exclusion criteria for the study, the investigator will assess the suitability of the patient for enrollment into the study.

Results of this study will be disclosed according to the relevant regulatory requirements. All publications in peer-reviewed medical journals resulting from this study will be listed in the original study protocol registration record (e.g., on ClinicalTrials.gov).

VIII. Data Quality Assurance

All patient data relating to the study will be recorded on the eCRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with 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 10 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

IX. Source Documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data entered in the eCRF 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.

X. Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. 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 study-site closure visit has been performed.

The investigator may initiate study-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 but are not limited to:

- 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 patients by the investigator
- Discontinuation of further study treatment development

Appendix 6 Adverse Events: Definitions and Procedures

I. Definitions

Definition of an AE

An AE is any untoward medical occurrence in a patient or clinical study patient, temporally associated with the use of study treatment, whether or not considered related to study treatment.

NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.

Events Meeting the AE Definition

- Any clinically significant laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline. Laboratory tests are considered clinically significant, if:
  - Any criterion for an SAE is fulfilled
  - The abnormality causes the patient to discontinue from the study treatment
  - The abnormality causes the patient to interrupt the study treatment or a modification of dosing
  - The abnormality requires intervention as corrective treatment or consultation
  - The investigator judges that the abnormality is clinically relevant and should be reported as an (S)AE in the eCRF
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or severity of the condition
- New conditions detected or diagnosed after study treatment administration
- Signs, symptoms, or clinical sequelae of a suspected drug-drug interaction
- Signs, symptoms, or clinical sequelae of a suspected overdose of a study treatment constitute an SAE. Asymptomatic overdose must only be reported as an SAE if observed for pembrolizumab.
- Signs, symptoms, and/or clinical sequelae resulting from disease progression will be reported as AE or SAE if they fulfil the definition of an AE or SAE. The terms “disease progression”, “progressive disease”, or similar, per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments.

Events <u>NOT</u> Meeting the AE Definition

- The terms “progressive disease” or “progression of disease” per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments.

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.

Definition of an SAE

If an event is not an AE according to the above definition, then it cannot be an SAE even if seriousness conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening

Life-threatening in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death, if it were more severe.

- Required inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other seriousness criterion, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

- Results in persistent disability or incapacity

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly or birth defect
- Other situations:
  - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the

patient or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Definition of an Unexpected Adverse Drug Reaction

An unexpected adverse drug reaction is defined (as per ICH Topic E2A) as all noxious and unintended responses to a medicinal product related to any dose which nature or severity is not consistent with the relevant source document, i.e., current IB. When reported as serious, the unexpected adverse reaction is defined as suspected unexpected serious adverse reaction. The safety vendor is responsible for notifying suspected unexpected serious adverse reactions to health authorities and Independent Ethic Committees (IEC) in accordance with local regulations.

II. Recording, Evaluation, Follow-Up, and Reporting of an AE, Including AESIs and SAEs

Recording of AEs, Including AESIs and SAEs

- When an AE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE.
- The investigator will then record all relevant information in the eCRF.
- It is **not** acceptable that the investigator sends photocopies of the patient's medical records to the safety vendor in lieu of completion of the respective sections of the eCRF.
- There may be instances when copies of medical records for certain cases are requested by the safety vendor. In this case, all patient identifiers, with the exception of the patient number, must be redacted on the copies of the medical records before submission to the safety vendor.

SAE Reporting to the Safety Vendor via the eCRF

- The safety vendor for this study is IQVIA Pharmacovigilance and is responsible for SAE processing and reporting.
- The primary system for SAE reporting to the safety vendor is the eCRF.
- Investigators and other site personnel need to report all SAEs within 24 hours of first awareness. The same applies for follow-up information on SAEs.
- If the eCRF is unavailable, a paper SAE reporting form needs to be completed by the investigator or other relevant site staff, signed by the investigator, and faxed to +353 1 809 9501 or scanned and e-mailed to QLS_IFX1@iqvia.com.

- The site will enter the SAE data into the eCRF as soon as it becomes available.
- After the study is completed at a given site, the eCRF will be taken off-line to prevent the entry of new data or changes to existing data.
- Any new SAE information from a study patient after the eCRF has been taken off-line can be reported on the paper SAE form via fax line +353 1 809 9501 or email to QLS_IFX1@iqvia.com.

Assessment of Severity for AEs, Including AESIs and SAEs

The investigator will make an assessment of severity for each AE reported during the study and assign it to 1 of the following categories (NCI CTCAE v5.0):

- Grade 1 (Mild): asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2 (Moderate): minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL*
- Grade 3 (Severe/medically relevant but not immediately life-threatening); hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
- Grade 4 (Life-threatening): life-threatening consequences; urgent intervention indicated
- Grade 5 (Death): death related to AE

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

Assessment of Relationship to Study Treatment of AEs, Including AESIs and SAEs

- The investigator is obligated to assess the relationship of study treatment to each occurrence of an AE.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered, investigated, and reported.
- The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE, the investigator **must** document in the medical notes that he/she has reviewed the AE and has provided an assessment of relationship to study treatment.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the safety vendor. However, it is very important

that the investigator always makes an assessment of relationship to study treatment for every event before the initial transmission of the SAE data to the safety vendor.

- The investigator may change his/her opinion of relationship to study treatment in light of follow-up information and send a SAE follow-up report with the updated relationship assessment.

Follow-up of AEs, including AESIs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor or the safety vendor to elucidate the nature and/or relationship to study treatment of the AE comprehensively. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- In case of persisting AEs, follow-up must continue until the AEs have resolved to grade ≤1 or baseline or are deemed irreversible by the investigator.
- If a patient dies during participation in the study or during a recognized follow-up period, the investigator will provide the safety vendor with a copy of any post-mortem findings including histopathology, as applicable.

Appendix 7 Contraceptive Guidance and Collections of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP:

1. Premenarchal

23. Premenopausal female with 1 of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the patient's medical records, medical examination, or medical history interview.

24. Post-menopausal female:

- A post-menopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone level in the post-menopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single follicle stimulating hormone measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status before study enrollment.

Contraception Guidance

Male Patients

Male patients with female partners of childbearing potential are eligible to participate if they agree to ONE of the following during the study and [redacted] after last dose of IFX-1 or 120 days after last dose of pembrolizumab:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

- Agree to use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 3 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant

Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration [during the protocol-defined time frame].

Men must refrain from donating sperm for the duration of the study and for 3 months after the last dose of IFX-1 or 120 days after last dose of pembrolizumab.

Female Patients

Female patients of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception (from the day of study medication initiation [or 14 days prior to the initiation of study medication for oral contraception] throughout the study period and [redacted] for IFX-1 or 120 days for pembrolizumab after the last dose of study medication) consistently and correctly as described in Table 3.

Table 3 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] (failure rate of <1% per year when used consistently and correctly)
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: [b] • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent [a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation: [b] • Intrauterine device • Intrauterine hormone-releasing system • Bilateral tubal occlusion

Vasectomized partner: A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP, and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with study treatment. 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 patient.

a Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for patients participating in clinical studies.
b Hormonal contraception may be susceptible to interaction with study treatment, which may reduce the efficacy of the contraceptive method. In this case, 2 highly effective methods of contraception should be utilized during the treatment period and [redacted] after the last dose of IFX-1 or 120 days after last dose of pembrolizumab.

Pregnancy Testing

WOCBP who have a positive serum pregnancy test result within 7 days before treatment should be excluded.

Additional urine pregnancy testing will be performed Q2W during the treatment period and at the first follow-up visit for Arm A and the first follow-up visit and 120 days after the last dose of pembrolizumab for Arm B.

Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

Collection of Pregnancy Information

Male Patients With Partners who Become Pregnant

The investigator will attempt to collect pregnancy information on any male patient's female partner who becomes pregnant while the male patient is in this study. This applies only to male patients who receive IFX-1 or pembrolizumab.

After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and

child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Patients who Become Pregnant

The investigator will collect pregnancy information on any female patient who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a patient's pregnancy. The patient will be followed at least monthly to determine the outcome of the pregnancy. The investigator will collect follow-up information on the patient and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to study treatment by the investigator will be reported to the safety vendor as described in Appendix 6. While the investigator is not obligated to actively seek this information in former study patients, he or she may learn of an SAE through spontaneous reporting.

Any female patient who becomes pregnant while participating in the study will discontinue study treatment.

Appendix 8 Treatment Modification Guidelines

Table 4 Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events Associated with Pembrolizumab or IFX-1

General instructions:

1. Severe and life-threatening irAEs should be treated with intravenous corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembrolizumab must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last pembrolizumab treatment.
3. The corticosteroid taper should begin when the irAE is ≤Grade 1 and continue ≥4 weeks.
4. If pembrolizumab and IFX-1 have been withheld, pembrolizumab and/or IFX-1 may resume after the irAE decreased to ≤Grade 1 after corticosteroid taper.

irAEs	Toxicity Grade (CTCAE v5.0)	Action with pembrolizumab and IFX-1	Corticosteroid and/or other therapies	Monitoring and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor patients for signs and symptoms of pneumonitis • Evaluate patients with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea/Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	• Monitor patients for signs and symptoms of enterocolitis (i.e., diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e., peritoneal signs and ileus) • Patients with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Patients with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via intravenous infusion
	Recurrent Grade 3 or Grade 4	Permanently discontinue		
AST or ALT elevation or increased bilirubin	Grade 2 [a]	Withhold	Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)

	Grade 3 [b] or 4 [c]	Permanently discontinue	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• Initiate insulin replacement therapy for patients with T1DM • Administer antihyperglycemic in patients with hyperglycemia	Monitor patients for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Continue	Treat with nonselective beta-blockers (e.g., propranolol) or thionamides as appropriate	Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypothyroidism	Grade 2, 3, or 4	Continue	Initiate thyroid replacement hormones (e.g., levothyroxine or liothyronine) per standard of care	Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 2, 3 or 4	Permanently discontinue	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		

	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] AST/ALT: >3.0 - 5.0 × ULN if baseline normal; >3.0 - 5.0 × baseline, if baseline abnormal; bilirubin:>1.5 - 3.0 × ULN if baseline normal; >1.5 - 3.0 × baseline if baseline abnormal

[b] AST/ALT: >5.0 - 20.0 × ULN, if baseline normal; >5.0 - 20.0 × baseline, if baseline abnormal; bilirubin: >3.0 - 10.0 × ULN if baseline normal; >3.0 - 10.0 × baseline if baseline abnormal

[c] AST/ALT: >20.0 × ULN, if baseline normal; >20.0 × baseline, if baseline abnormal; bilirubin: >10.0 × ULN if baseline normal; >10.0 × baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab and/or IFX-1 is at the discretion of the investigator or treating physician. If control achieved or ≤Grade 2, pembrolizumab and/or IFX-1 may be resumed.

[e] Events that require discontinuation include but are not limited to: encephalitis and other clinically important irAEs (eg. vasculitis and sclerosing cholangitis).

Table 5 Dose Modification and Toxicity Management Guidelines for Infusion-Related Reactions Associated with Pembrolizumab or IFX-1

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	• Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, intravenous fluids); prophylactic medications indicated for ≤24 hrs.	• **Stop Infusion.** • Additional appropriate medical therapy may include but is not limited to: • Intravenous fluids • Antihistamines • Non-steroidal anti-inflammatory drugs • Acetaminophen • Narcotics • Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. • If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr. to 50 mL/hour). Otherwise dosing will be held until symptoms resolve and the patient should be premedicated for the next scheduled dose. **Patients who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study treatment**	Patient may be premedicated 1.5 hour (±30 minutes) prior to infusion of study treatment with: diphenhydramine 50 mg orally (or equivalent dose of antihistamine)., acetaminophen 500-1000 mg orally (or equivalent dose of analgesic)
Grades 3 or 4 **Grade 3:** Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) **Grade 4:** Life-threatening; pressor or ventilator support indicated	• **Stop Infusion.** • Additional appropriate medical therapy may include but is not limited to: • Epinephrine** • Intravenous fluids • Antihistamines • Non-steroidal anti-inflammatory drugs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids • Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. • Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Patient is permanently discontinued from further study treatment.	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

Appendix 9 Eastern Cooperative Oncology Group

Grade	Description
0	Fully active; able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; e.g., light housework, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about >50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair ≥50% of waking hours
4	Completed disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead

Source: Oken et al., 1982

Appendix 10 List of Vendors

Legal name of 3rd Party	Business address				Study activity performed
	Street	City	Zip Code	Country	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IFX-1 measurement, C3a measurement
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ADA measurement
InflaRx GmbH	Winzerlaer Str. 2	Jena	07745	Germany	C5a measurement
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IMP packaging, QP release and distribution
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXRS
PSI CRO AG	Baarerstr. 113a	Zug	6300	Switzerland	Feasibility & Site Identification, Project management, Site Management, Clinical Monitoring, Vendor Management, Medical Monitoring, Development of Study Documents, Regulatory, Trial Master File
Metronomia Clinical Research GmbH	Paul-Gerhardt-Allee 42	Munich	81245	Germany	EDC system, Data Management, Statistical Analysis
IQVIA Ltd.	Green Park, 500 Brook Drive	Reading Berkshire	RG2 v6UU	United Kingdom	Safety Management
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Image collection, QC, and storage until decision for or against central imaging read
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Kitting and Shipment of lab samples, Biomarker Analysis