PRODUCT OBSERVATIONAL STUDY PROTOCOL

Two cohort registry study for patients with advanced CSCC treated with Cemiplimab or other approaches

COMPOUND: Cemiplimab (SAR439684)

STUDY NUMBER: OBS16381

STUDY NAME: *CemiSkin*

The Study is conducted by

Sanofi-Aventis Deutschland GmbH

Brüningstr. 50

65926 Frankfurt

Version Number: 2.0

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NAMES AND ADDRESSES OF

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

Below are the details of the changes to the observation plan.

DOCUMENT HISTORY

Document	Country/Countries impacted by amendement	Date, version
Amended Observational Protocol V2.0	All countries	29-Oct-2021, Version 2.0
Observational Protocol V1.0	All countries	09-Jan-2020, Version 1.0

AMENDED PROTOCOL V2.0 (29-Oct-2021)

This amended Observational Protocol (V2.0) is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it does not significantly impact the safety or physical/mental integrity of participants, nor the scientific value of the study.

OVERALL RATIONALE FOR THE AMENDMENT

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Names & Addresses of Study Management	[redacted]	New address as of mid of December 2021
Names & Addresses of Study Management	Global statistician changed to the local statistician	Global Statistician no longer available
Names & Addresses of Country Teams representative	[redacted]: Change of clinic address	[redacted] been working at the Johannes Wesling Klinikum Minden since 01.04.21
Names & Addresses of Country Teams representative	Instead o[redacted] is Country Team Representative in Switzerland	New Country Team Representative in Switzerland
Names & Addresses of Scientific Director	[redacted]: Change of clinic address	[redacted] been working at the Johannes Wesling Klinikum Minden since 01.04.21
Names & Addresses of Sponsor	Sanofi-Aventis GmbH, Österreich: Twin Tower A, 29. Stock, Wienerbergstr. 11, A-1100 Wien	Clarification of the name of the sponsor and new address as of 01.12 2021
1 Synopsis Scientific Committee Chair Person	Instead of [redacted] is Scientific Committee Chair Person in Switzerland	New Scientific Committee Chair Person in Switzerland
1 Synopsis Study Design and Duration	"Sanofi-ICF" is used instead of "ICF"	Clarification that the Sanofi-ICF is only required for the prospective cohort

Section # and Name	Description of Change	Brief Rationale
1 Synopsis Study Population Inclusion criteria	Retrospective Cohort: no Sanofi-ICF is needed	Clarification that the Sanofi-ICF is not required for the retrospective cohort
1 Synopsis Study Population Inclusion criteria	Retrospective Cohort: including patients who are no longer alive	Clarification that it is planned to include patients in retrospective cohort who are no longer alive
1 Synopsis Main Data Collected retrospective cohort	Retrospective Cohort: no Sanofi-ICF is needed	Clarification that the Sanofi-ICF is not required for the retrospective cohort
1 Synopsis Main Data Collected retrospective cohort	Retrospective Cohort: including patients who are no longer alive	Clarification that it is planned to include patients in retrospective cohort who are no longer alive
1 Synopsis Estimated Duration of the Study	FPI changed to 01.03.21, LPI changed to 01.03.23, LPO changed to 01.03.26	Adjustment of data after delayed enrollment of the 1st patient in Germany
7.2 Study Duration and Dates	FPI (start of documentation) changed to 01.03.21, LPI changed to 01.03.23, LPO (end of documentation) changed to 01.03.26, Data base lock changed to 01.05.26, estimated clinical study report changed to 01.01.27	Adjustment of data after delayed enrollment of the 1st patient in Germany
8.2 Selection of patients – Inclusion criteria	Retrospective cohort: Change of > 18 years to ≥ 18 years and including patients who are no longer alive	Correction and Clarification
8.3 Selection of patients – Exclusion criteria	Retrospective cohort: advCSCC of unknown primary origin	Inserting a missing paragraph
8.3 Selection of patients - Premature withdrawal from the study	no Sanofi-ICF is needed	Clarification that the Sanofi-ICF is not required for the retrospective cohort
9 Case Report Form (CRF) Definitions for the CRF – Clinical Outcomes	TTNT: Change from "start of next medication" to "start of next systemic therapy"	Clarification
13 Management and reporting of adverse events/adverse reactions	“Alcedis” instead of “Aldedis”	Correction of a spelling mistake
13.3 AE of special interest (AESI)	“CRO” instead of “r”	Correction of a spelling mistake
14.3.1.1 primary variable	Change from "start of next medication" to "start of next systemic therapy”	Clarification
	All next systemic treatments excluding BSC will be evaluated	Insertion of the sentence for further explanation

1 SYNOPSIS

COMPOUND: Cemiplimab (SAR439684) **STUDY No: OBS16381**	
TITLE	**Two cohort registry study for patients with advanced CSCC treated with Cemiplimab or other approaches**
LOCATION	Approx. 60 sites in Germany, plus 5 sites in Switzerland and 5 sites in Austria
SCIENTIFIC COMMITTEE CHAIR PERSON	[redacted]
STUDY OBJECTIVE(S)	The objectives of the study are **Prospective cohort:** • To identify TTNT • To identify potential determinants of disease progression as final outcome, Quality of life (QoL), pain and other health related outcomes for CSCC patients undergoing treatment with Cemiplimab • To collect long-term effectiveness and describe effects of treatment • To collect safety data in a real world setting **Retrospective cohort:** • To examine real-world data of advanced CSCC (advCSCC) patients who were treated before approval of Cemiplimab (treatment approaches, safety, patient characteristics, long-term effects) **Primary objective prospective and retrospective cohort:** Primary objective for this non-interventional study (NIS) is time to next treatment (TTNT) excluding best supportive care (BSC). **Secondary objectives prospective cohort:** Patient demographics and baseline characteristics (TNM stage), Cemiplimab treatment regimen, duration of treatment (DOT), prior and post Cemiplimab treatments, response to Cemiplimab treatment (ORR, CR, PR, SD) , duration of response (DOR), disease control rate (DCR = CR+PR+SD), time to treatment failure (TTFT), overall survival (OS), progression free survival (PFS), safety data, quality of Life (QoL) incl. pain. **Secondary objectives retrospective cohort:** Patient demographics and baseline characteristics (TNM stage), effectiveness (ORR, PFS, OS) and safety of different treatment options used routinely for advanced CSCC prior to Cemiplimab launch, patterns

	of treatment.
STUDY DESIGN & DURATION	This is a non-interventional multicenter study in Germany, Austria and Switzerland. The study includes two cohorts of adult patients with advCSCC who receive either treatment with Cemiplimab (prospective cohort) or other therapeutic approaches (retrospective cohort). Enrollment will take place at approx. 70 study sites. The selection of participating sites will attempt to capture a representative sample of advCSCC treating clinic and office based physicians to get data from a real world setting outside of clinical trials. In each cohort 200 patients will be enrolled from Germany, Austria and Switzerland. The duration of follow up will be up to 36 months for each patient in the prospective cohort. Patients who meet the inclusion criteria and have signed the informed consent form (Sanofi-ICF) (only in the prospective cohort) will be included in the study.
STUDY POPULATION	**Inclusion Criteria** **For the prospective cohort:** a. Planned treatment with Cemiplimab for advCSCC according to SmPC b. Able to understand and complete study-related questionnaires c. Signed ICF **For the retrospective cohort:** d. Patients ≥ 18 years with first diagnosed advCSCC (locally advanced or metastatic CSCC) between Jan/2012 and Aug/2019 e. From these patients only anonymous data will be collected. Thus no Sanofi-ICF is needed This procedure allows including data from patients who are no longer alive (planned). **Exclusion Criteria** **For the prospective cohort:** a. Missing ICF b. advCSCC of unknown primary origin c. Any condition that, in the opinion of the study physician, may interfere with patient's ability to participate in the study, such as severe cognitive impairment or other comorbidities that would, in the opinion of the study physician, predictably prevent the patient from adequately completing QoL assessments.

	For the retrospective cohort: d. Patients enrolled in clinical trials with Cemiplimab for advCSCC treatment e. advCSCC of unknown primary origin **Sample Size:** 400 patients (200 patients in each cohort)
RECRUITMENT MODALITIES	**Selection of Physicians/sites** Study site selection will be performed independently in Germany, Austria and Switzerland. This study will be conducted among sample representatives who are advCSCC-treating physicians (e.g., Dermatology- Oncologists, Oncologists, Surgeons). Physicians will be recruited from country-specific physician databases and ADOReg (ADO, Arbeitsgemeinschaft Dermatologische Onkologie; Reg, Registry). **Selection of patients** These physicians or their assigned staff will be responsible for patient chart identification, qualification and selection, data abstraction, completion of the patient eCRF, resolution of data queries and data validations.
STUDY TREATMENT	No investigational agents due to the non-interventional character of the study. Patients may receive any therapies as deemed necessary by their treating physicians for the treatment of advCSCC or other comorbid conditions.
ENDPOINTS / OUTCOMES	Data will be summarized descriptively with consideration for the following outcomes of interest: **Primary Endpoint:** Effectiveness o The primary endpoint is TTNT excluding best supportive care (BSC) **Secondary Endpoints:** Health related outcomes and safety o Secondary endpoints include health related outcomes such as ORR, DOR, DCR, QoL, OS, PFS, pain and safety data.
MAIN DATA COLLECTED	**Prospective cohort:** Each patient will be initially treated with Cemiplimab and documented during a follow up time of 36 months according to the usual follow-up in the routine practice. Documentation will be performed up to 8 times: • D1: Baseline • D2: after approx. 3 months • D3: after approx. 6 months • D4: after approx. 9 months

	• D5: after approx.12 months • D6: after approx. 18 months • D7: after approx. 24 months • D8: after approx. 36 months / end of the Study In case of Cemiplimab treatment discontinuation in the eCRF at any time, the documentation will continue until D8 or patient´s death to assess outcome and further therapeutic modalities, unless the patient withdraws the consent. The collected data will include: • Patient and Tumor Characteristics: o Demographics (Gender, age ect.) o Past medical history, regarding anti-tumor treatment prior to Cemiplimab, o Disease staging o Risk factors related to advCSCC progression and survival • Survival: o advCSCC specific and overall mortality • Treatment Patterns: o Interventions for advCSCC treatment (e.g., surgery, radiation, drug therapy, etc.) before initiation of Cemiplimab, if applicable o Patterns of recurrence o Determinants for disease sequela (recurrence, metastasis) o • Patient Reported Outcomes: o Baseline QoL o Baseline health status o Impact of Cemiplimab on QoL based on EORTC QLQ-C30 questionnaire • Response: o Time to next treatment (TTNT) or death o Objective response rate (ORR) o Progression free survival (PFS) o Disease Control Rate (DCR) o Duration of Response (DOR) o Duration of Treatment o Overall Survival (OS) o Immune-related adverse events (irAEs) o Serious adverse events (SAEs) o Disease Specific Death Rate (DSD) **Retrospective Cohort:** In the retrospective cohort this study will document (1 documentation time point) patients not intended for Cemiplimab therapy and first diagnosed with advCSCC between Jan/2012 and Aug/2019. It will obtain data of anti tumor therapies (prior to Cemiplimab approval) and

<table>
<tr><td></td><td>their outcome. We plan to document the disease history including prior surgery, radiotherapy, systemic therapies and the related safety data as well as effectiveness. The largest study with advCSCC was recently published (Hillen et al. 2018), which examined retrospectively 190 patients from Germany and Austria first diagnosed between Jan/2010 and Dec/2011 with a first-time follow-up on May/2014.

Within this retrospective cohort, we will collect only anonymous data from patients without Sanofi-ICF. This procedure allows including data from patients who are no longer alive (planned)

Patient characteristics (age, sex, diseases, immunosuppression, comorbidities, localization, etc.) and therapeutic modalities will be evaluated (as in the prospective cohort if applicable).</td></tr>
<tr><td>STATISTICAL METHODOLOGY</td><td>Sample size justification

The primary objective of the study is to describe TTNT or death in 200 patients with advCSCC initially treated with Cemiplimab (prospective cohort) or 200 patients with other therapeutic approaches (retrospective cohort).

<table>
<tr><th>Sample size</th><th>Number of event</th><th>With of 95%CI</th><th>Median TTNT (months)</th><th>Lower limit 95% CI</th><th>Upper limit 95% CI</th></tr>
<tr><td rowspan="3">200</td><td rowspan="3">180</td><td>8.9</td><td>30.0</td><td>26.1</td><td>34.9</td></tr>
<tr><td>11.8</td><td>40.0</td><td>34.7</td><td>46.6</td></tr>
<tr><td>14.8</td><td>50.0</td><td>43.4</td><td>58.2</td></tr>
</table>
References Mathews, Paul. 2010. Sample Size Calculations: Practical Methods for Engineers and Scientists. Mathews Malnar and Bailey, Inc.

Including 200 patients in each cohort produces a two-sided 95% confidence interval with a width equal from 8.9 to 14.8 when the expected median TTNT is respectively from 30 to 50 monts. The percent censoring is anticipated to be 10%.

Primary analysis

The primary analysis is descriptive. TTNT will be estimated and visualized for each cohort separately by Kaplan-Meier estimators. Median TTNT will be presented with 95%-confidence intervals. Potential predictors of TTNT will be analyzed using Cox proportional hazards regression.

Secondary analysis

All secondary outcomes will be analyzed descriptively.

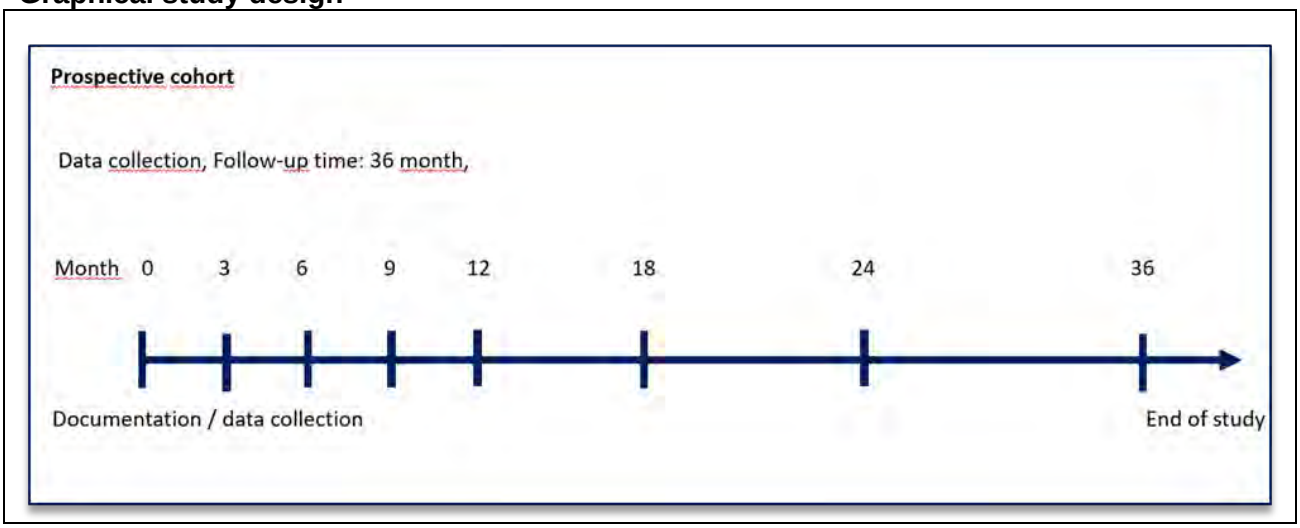
The rate of ORR and 95%-CI will be given for each cohort. In addition</td></tr>
</table>

	and in an exploratory way, the pooled rate and its 95%-confidence interval will also be given. Potential predictors of response will be analyzed using logistic regression and/or Factorial Multiple Correspondences Analyses. For time to event endpoints, Kaplan-Meier curves will be presented and median time to event will be estimated with corresponding 95%-confidence intervals.
ESTIMATED DURATION OF THE STUDY	**Prospective cohort:** Estimated enrollment duration 24 months Estimated dates: o First Patient In: 01.03.2021 o Last Patient In: 01.03.2023 o Last Patient Out: 01.03.2026 **Retrospective cohort:** Patients first diagnosed with advCSCC between Jan/2012 and Aug/2019 and not intended to receive Cemiplimab will be documented in the retrospective cohort once.

2 FLOW CHARTS

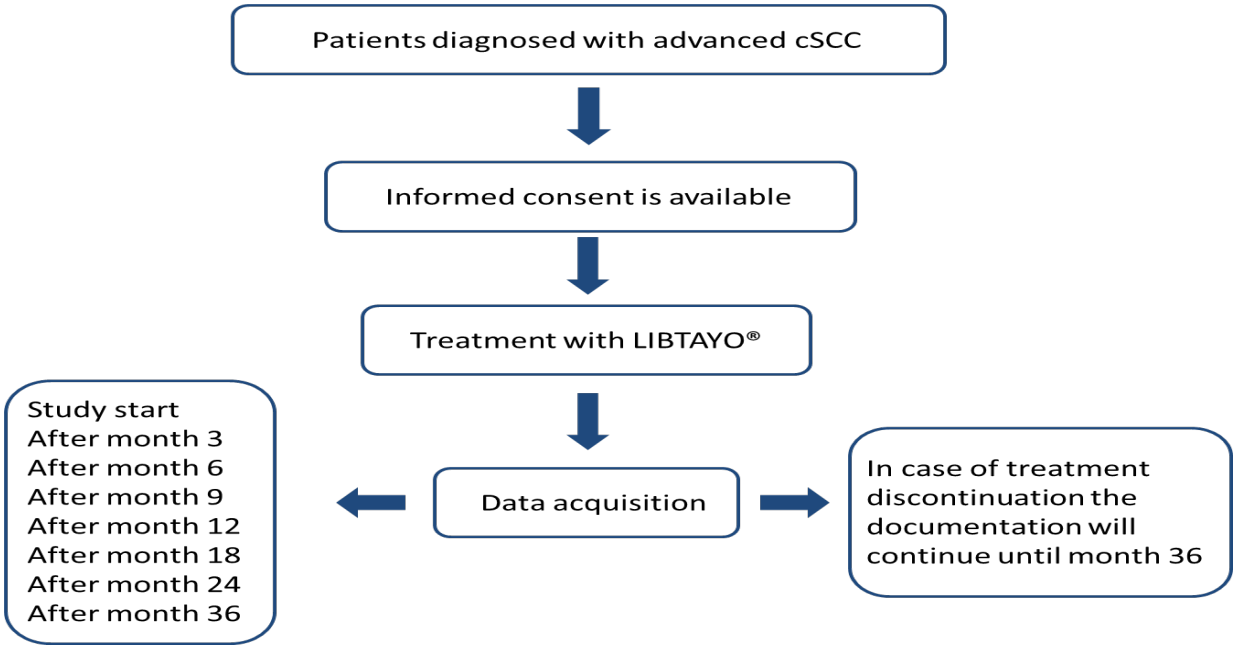
2.1 GRAPHICAL STUDY DESIGN

Graphical study design



2.2 STUDY FLOW CHART

Study flow chart of the prospective cohort



3 TABLE OF CONTENTS

4 LIST OF ABBREVIATIONS

advCSCC	advanced cutaneous Squamous Cell Carcinoma
AE	Adverse event
BCC	Basal cell carcinoma
BSC	Best supportive care
CR	Complete response
CRF	Case report form
cCRF	electronic Case report form
CRO	Clinicial research organization
CSCC	Cutaneous squamous cell carcinoma
DOR	Duration of response
DOT	Duration of treatment
DSD	Disease specific death rate
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
H&N	Head and neck
ICF	Informed consent form
irAE	Immune related adverse event
ladvCSCC	locally advanced cutaneous squamous cell carcinoma
LOT	line of therapy
mCSCC	metastasized cutaneous squamous cell carcinoma
NIS	Non-interventional study
NMSC	Non-melanoma skin cancer
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PR	Partial response
QLQ	Quality of life questionnaire
QoL	Quality of life
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAP	Statistical analysis plan
SCI	Skin Cancer Index
SD	Stable disease
SmPC	Summary of product characteristics
SoC	Standard of care
TTNT	Time to next treatment
TTTF	Time to treatment failure

5 INTRODUCTION AND RATIONALE

5.1 INTRODUCTION

Nonmelanoma skin cancer (NMSC) is the most common malignancy worldwide, consisting primarily of basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (CSCC). CSCC makes approximately 20% of all NMSC cases (Stratigos A, 2015). CSCC is generally more aggressive than BCC, with a higher likelihood of becoming ladvCSCC or mCSCC (Rogers HW, 2010). The exact incidence of CSCC is unknown, as registries do not track all cases. However, the lifetime risk for developing CSCC is estimated to be 7%–11%, with dramatic observed increases over recent decades (Miller DL, 1994).

About 16,881 new cases in men and 14,855 cases in women of CSCC were estimated in Germany 2013 (40 / 100,000 people per year resulting in 32,000 CSCC patients anually) (Leiter U, 2014). A high incidence rate is also found in Switzerland (28.9 / 100,000 person per year) (Hollestein LM, 2012; Xiang F, 2014). Although overall CSCC incidence is common, only a small percentage of approx. 5% is expected to progress to mCSCC or ladvCSCC. The majority of CSCC patients can be managed with local therapies (Lippman SM, 1992). The remaining 5% of patients are at high-risk for locally advanced disease and metastazised CSCC. The estimated five-year rate of CSCC recurrence is 8% (Stratigos A, 2015; Levine DE, 2015; Thompson AK, 2016). Larger primary lesions (> 2 cm in diameter), higher histologic grade, particularly thicker lesions, and immune suppressed individuals are considered to be at higher risk for metastasis, with occurrence estimated between 2–5% of patients (Stratigos A, 2015; Thompson AK, 2016). The CSCC lethality rate is difficult to estimate in part due to inaccurate incidence estimates. In Australia the estimated mortality rate is approximately 5%, whereas U.S. studies suggest a rate of 1% (Joseph MG, 1992; Clayman GL, 2005). No standard treatment regimen for advCSCC (mCSCC or ladvCSCC) has been established and tumors are often managed similarly to head and neck SCC. Therefore, patients with advanced disease have a poor survival prognosis. In general, the approach to management relies on surgically removing “satellite or in-transit” metastases around the primary tumor if complete removal is possible. In those with unresectable CSCC, treatment is difficult. A partial response was shown in 44% and a SD in 24% of patients with previuously available therapies (Jarkowski et al. 2016). The evidence for effectiveness of currently available systemic therapies for advCSCC is limited to case studies and phase 2 studies with low patient numbers. Generally, advCSCC is chemo responsive; but responses are usually very short-lived and connected to high toxicity, especially in the predominantly elderly patient population.

Radiation therapy alone or in combination with chemotherapy may be used as an alternative option when surgery is not feasible (Stratigos A, 2015). With limited survival, advCSCC (mCSCC and ladvCSCC) have a high unmet medical need (Karia PS, 2013).

Evidence for Cemiplimab in advCSCC

Substantial progress has recently been made in the development of immunotherapy for the treatment of cancer and specifically advCSCC. Checkpoint-blockade uses antibodies that impede immune inhibitory pathways such as programmed cell death 1 (PD-1) or PD-1 ligand 1 (PD-L1) interaction (Chang ALS, 2016). Efforts to characterize the genetic landscape of CSCC have been hampered by very high background mutation rates associated with UV damage which can be 5 to 15 times higher than what is found for non-cutaneous tumors. And with understanding the genomic signatures of aggressive CSCC it provides an opportunity to intensify upfront therapies in order to prevent the morbid consequences of treating advanced disease (Pickering 2014).

Cemiplimab is a high affinity, fully humanized, hinge stabilized IgG4P antibody against the PD-1 receptor that blocks the interaction of PD-1 with its ligands, PD-L1 and PD-L2 (Migden MR, 2018). Cemiplimab was approved by the FDA (Sep/2018) and by the EMA (June 28th 2019) for the treatment of adult patients with advCSCC who are no candidates for curative surgery or curative radiation [SmPC, Fachinformation LIBTAYO (Cemiplimab), September 2019], and is being studied in several other indications.

The efficacy of Cemiplimab in patients with mCSCC (nodal or distant) or ladvCSCC who were not candidates for curative surgery or curative radiation was evaluated in two open label, multicenter, non-randomized, multicohort studies: Study 1423 (NCT012383212) and 1540 (NCT01760498) (Kaplon H 2018, Papadopoulos KP 2016). Patients received Cemiplimab 3 mg/kg intravenously every 2 weeks for up to 48 weeks in study 1423 and up to 96 weeks in study 1540. In study 1540 one group with mCSCC patients were treated with a fix dose of 350mg every 3 weeks. The major efficacy outcome measure was confirmed by ORR. The efficacy analysis was conducted when all patients had the opportunity for at least 6 months of follow up. At the time of data cut-off (October 27th 2017) 47% of patients with mCSCC showed an objective response to Cemiplimab in study 1540, with a mean observed time to response of 1.9 months. The ORR in76 locally advCSCC was 43.6% (data cut-off October 10th 2018) (Migden et al., ASCO 2019). At the time of data cut-off (September 20th 2018) PFS was 18.4 months in 59 mCSCC treated with cemiplimab (Guminski et al., ASCO 2019).

5.2 RATIONALE

Given the drastic shift in the therapy options for advCSCC with the approval of Cemiplimab for the treatment of mCSCC and ladvCSCC, it is important to gain a better understanding of the changing paradigms in treatment of these patients. Gathering data in the time-frame before and after the approval of Cemiplimab for the therapy of advCSCC will allow for an assessment of therapy outcomes in a real-world setting.

Therefore, via this longitudinal two-cohort study with a prospective and a retrospective cohort, we will characterize patients and disease characteristics, survivorship, real-world treatment patterns and clinical outcomes among adult patients diagnosed with advCSCC (mCSCC and ladvCSCC).

6 STUDY OBJECTIVES

The principal objective of the Cemiplimab NIS with two cohorts is to examine real-world data of advCSCC patients undergoing treatment with Cemiplimab to identify potential determinants of disease progression, QoL, and other health related outcomes for advCSCC patients in a real-world setting.

The objective of this NIS is to collect and describe long-term effectiviness and safety of treatment with Cemiplimab.

Primary objectives

Prospective and retrospective cohort: Primary objective for this Cemiplimab NIS is to evaluate the clinical outcomes in treatment of advCSCC as a result of TTNT. Assessments of the response are clinical observations of physician's choice.

Secondary objectives of the prospective cohort

- DOR to identify and describe long-term effects of treatment of patients with CSCC
- DCR (CR+PR+SD) at 3, 6, 9, 12, 18, 24, 36 months
- To assess patient experience, functional status, QoL and pain, in a real-world setting for patients with advCSCC at 3, 6, 9, 12, 18, 24 and 36 months
- To collect and describe safety data on study participants
- To describe patients who receive Cemiplimab as treatment for advCSCC in a real-world setting
- OS defined as duration from current mCSCC or ladvCSCC diagnosis and also from the initiation of each LOT until death or end of follow up
- Proportion of patients surviving at month 3, 6, 9, 12, 18, 24 and up to months 36 from initiation of systemic therapy
- PFS defined as time from first documented systemic cemiplimab therapy initiation until progression or treatment discontinuation due death or end of follow up
- Patient demographics and baseline characteristics (incl. age, performance status etc.) at study entry
- Characterization of Cemiplimab usage patterns
- Cemiplimab treatment regimen (initial dose and date of initiation and regimen changes)
- Treatment prior to and post Cemiplimab treatment, incl. surgery, radiation, systemic therapies incl. agents administered, dose, frequency and duration

- Surgery post initiation of Cemiplimab treatment
- DOT
- TNM stage (AJCC or UICC)
- Analysis of Cemiplimab tolerability and safety profile in daily clinical practice
- Observed rates, reasons and timing of the discontinuation of Cemiplimab
- TTTF including lack of response and discontinuation due to AE
- Analysis of change in patient reported QoL as per EORTC-QLQ-C30 QoL questionnaire during treatment with Cemiplimab (for prospective cohort only)

Secondary objectives of the retrospective cohort

- Description of retrospective patient population, patterns of care and effectiveness of different treatment options used under routine conditions for advanced CSCC prior to Cemiplimab launch
- To collect and describe safety data on study participants
- Proportion of patients surviving at month 3, 6, 9, 12, 18, 24 and up to months 36 from initiation of systemic therapy
- PFS defined as time from first documented systemic therapy initiation until progression or treatment discontinuation due death or end of follow up
- Patient demographics and baseline characteristics (incl. age, performance status etc.) at study entry
- TNM stage (AJCC or UICC)
- Patterns of treatment for the retrospective cohort.

7 STUDY DESIGN

7.1 DESCRIPTION OF THE STUDY DESIGN

This is an observational study with two cohorts (prospective and retrospective) of adult patients with advCSCC. No study intervention will be performed. It is an international multicenter study of Germany, Austria and Switzerland.

Prospective cohort:

Each patient will be initially treated with Cemiplimab and documented during a follow up time of 36 months. Documentation will be performed up to 8 times (D1: Baseline, D2: after approx. 3 months, D3: after approx. 6 months, D4: after approx. 9 months, D5: after approx.12 months, D6: after approx. 18 months, D7: after approx. 24 months, D8: after approx. 36 months / End of the Study). In case of Cemiplimab treatment discontinuation at any time, the documentation will continue until D8 or patient's death to assess outcome and further therapeutic modalities.

The prospective cohort of this observational study plans to collect patients with mCSCC – defined as patients with local/regional (nodal metastasis, field cancerization ect.) as well as distant metastasis (also distant lymph-node), and ladvCSCC – defined as patients that could not be cured either by curative surgery, curative radiotherapy or both based on a decision of an interdisciplinary tumor board. These patients will receive treatment with Cemiplimab within their clinical routine treatment.

At each participating study site, all advCSCC patients who will initiate treatment with Cemiplimab in a real-world setting will be eligible to participate in the study until the enrollment goal is achieved. The decision to prescribe Cemiplimab will be based solely on the treating physician's clinical judgment. Patients who meet inclusion criteria according to SmPC of Cemiplimab and have signed the ICF will be included in the study.

Retrospective cohort:

Patients first diagnosed with advCSCC between Jan/2012 and Aug/2019 will be included and documented at study entry with anonymous data.

Informed Consent Form (ICF)

It is the responsibility of the physician or designee to obtain written ICF from each compliant patient of the prospective cohort prior to the documentation of his / her data in the eCRF. One original ICF must be retained by the study site as part of the patient's study record, and another original of the signed ICF must be given to the patient. The ICF must be provided before the patients data are documented in the eCRF.

Enrolled patients who initiate treatment with Cemiplimab will complete baseline QoL assessments at the time of ICF, and will continue with subsequent assessments at their Cemiplimab dosing and advCSCC standard of care (SoC) visits for up to 3 years. Additional procedures will be performed as dictated by the local SoC, as deemed necessary by the treating physician based on usual care. Data collection will mirror SoC procedures relating to the patient's treatment. Patients will remain eligible and will be encouraged to stay in the study if they discontinue Cemiplimab (permanently or temporarily). Once enrolled, patients will remain in the study until further participation is declined.

In the study the data to support the primary objectives are abstracted from medical records for patients with advCSCC (ladvCSCC or mCSCC), living or deceased, from the time of advCSCC diagnosis (i.e., index date) until the most recently documented visit, death, or lost to follow up whichever comes later. Specifically, data on treatment patterns prior to date of first mCSCC or ladvCSCC diagnosis, as far as data permits will be collected to support the secondary objectives.

7.2 DURATION OF STUDY PARTICIPATION FOR EACH PATIENT

In the prospective cohort the data will be recorded during a follow-up of 36 months, beginning after study inclusion.

In the retrospective cohort we will document at one time point patients not intended for Cemiplimab therapy, who were first diagnosed advCSCC between Jan/2012 and Aug/2019. QoL data will be collected from patients within the prospective cohort. It is planned to perform yearly interim analyses and a final report at the end of the study.

Study duration and dates

- Estimated enrolment duration: 24 months
- Start of documentation: 01.03.2021
- Estimated follow up: up to 8 documentation points within 36 months
- Last patient In: 01.03.2023
- Last patient Out/End of documentation 01.03.2026
- Database lock planned date: 01.05.2026
- Estimated Report date: 01.01.2027

The starting dates of this NIS will differ in Germany, Austria and Switzerland according to the operational set up.

7.3 EVALUATION CRITERIA

Study examinations will take place at months 3, 6, 9, 12, 18, 24 and 36.

Survey of concomitant medication and Cemiplimab treatment will take place at all study examinations.

Tumor Evaluation will be conducted according to guidelines and evaluation according to RECIST v.1.1 (Appendix 16.2). Computed tomography (CT) scan or magnetic resonance imaging (MRI) of chest, abdomen and pelvis and additional tumor bearing areas as well as digital photography of cutaneous lesions are preferred methods.

Adverse Events

Evaluation of Severity

The severity of SAEs will be graded using the Common Terminology Criteria for AE (CTCAE)5.0 as documented in the medical record.Questionnaire: EORTC – QoL Core 30.

The investigator should assess irAE severity based on the nature of the event, intensity of signs and/or symptoms, current functional impairment, and potential long-term health hazards related to the event. The following scale is provided only as general guidance:

- **Mild:** Does not interfere in a significant manner with the patient's normal functioning level. It may be an annoyance. Prescription drugs are not ordinarily needed for relief of symptoms, but may be given because of personality of the patient.
- **Moderate:** Produces some impairment of functioning but is not hazardous to health. It is uncomfortable or an embarrassment. Treatment for symptom may be needed.
- **Severe:** Produces significant impairment of functioning or incapacitation and is a definite hazard to the patient's health. Treatment for symptom may be given and/or patient hospitalized.

Evaluation of Causality

The investigator should assess the potential relationship between the irAE or SAE and patient's treatments, which could be medications or medical procedures administered for

CSCC or for any other condition. There are 2 alternative (mutually exclusive) options for this assessment. Select the one that appears most likely:

- **Not treatment-related:** The irAE/SAE occurred independently of any of the patient's treatments. An alternative cause is suspected, or otherwise there is no reason to suspect that one or more of the patient's treatments may have caused the irAE/SAE

- **Treatment-related:** The irAE/SAE was likely caused by one or more of patient's treatments

If treatment-related, the suspected treatment(s) should be identified.

8 SELECTION OF PATIENTS

This section outlines definitions of the specific patient population evaluated in this observational study and the patient selection criteria.

8.1 SAMPLE SIZE

Considering the fact that this is a descriptive study, there must be no testing of an *a priori* hypothesis. In our study the primary objective is to describe TTNT or death in 200 patients with advCSCC initially treated with Cemiplimab (prospective cohort) or 200 patients with other therapeutic approaches (retrospective cohort). Sample size justification is described in detail in our synopsis section “STATISTICAL METHODOLOGY.”

Approximately 60 participating expert centers located in Germany, and 5 centers from each Austria and Switzerland respectively will participate in the study. Participating centers will include different professional groups with permission for systemic treatment either in university clinics or an office-based setting to get a representative picture of the real-world advCSCC treatment.

Definition of the patient cohorts

For this observational study, data will be collected for two cohorts, a prospective cohort and a retrospective cohort. In both cohorts, data of advCSCC patients with mCSCC or ladvCSCC will be collected.

The mCSCC cohort is defined as those with locoregional nodal as well as distant metastasis.

The lacSCC cohort is defined as patients that could not be treated with a curative intent either by surgery, radiotherapy or both based on a decision of an interdisciplinary tumor board.

8.2 INCLUSION CRITERIA

Prospective cohort:

- Planned treatment for advCSCC adult patients ≥ 18 yrs who are at the first time initiated on Cemiplimab treatment according to SmPC of Cemiplimab
- Able to understand and complete study-related questionnaires
- Signed ICF

Retrospective cohort:

- Patients ≥ 18 years with advCSCC first diagnosed between Jan/2012 and Aug/2019
- From these patients only anonymous data will be collected. Thus no Sanofi-ICF is needed. This procedure allows including data from patients who are no longer alive (planned).

8.3 EXCLUSION CRITERIA

Prospective cohort:

- Missing ICF
- advCSCC of unknown primary origin
- Any condition that, in the opinion of the investigator, may interfere with patient's ability to participate in the study, such as severe cognitive impairment or other comorbidities that would, in the opinion of the investigator, predictably limit compliance with the intended treatment plan, or prevent the patient from adequately completing QOL assessments.

Retrospective cohort:

- Patients enrolled in clinical trials for advCSCC treatment
- advCSCC of unknown primary origin

Premature withdrawal from the study

A patient has the right to withdraw from the study at any time, for any reason, and without any penalties resulting from this decision.

The participating physician should make every effort to re-contact the patient to determine his/her health status, including at least his/her vital status. In case of Cemiplimab treatment discontinuation at any time, the documentation will continue until month 36 or patient's death to assess outcome and further therapeutic modalities.

For the retrospective cohort: no Sanofi-ICF will be collected.

Study completion

Prospective cohort: Each patient will be considered to have completed this study at the time they complete 3 years of follow up at the time they withdraw consent for further participation, or at the time of death.

Patients will remain in the study even if they discontinue cemiplimab permanently or temporarily.

Patients who discontinue treatment and/or choose not to continue with follow up visits and questionnaires will still be followed for survival at 3 month intervals, provided they do not withdraw their consent completely for the full 3 years duration of follow-up.

8.4 MODALITIES OF RECRUITMENT

Selection of sites

Study site selection will be performed independently in Germany, Austria and Switzerland.

This study will be conducted among sample representatives who are advCSCC-treating physicians (e.g., Dermatology Oncologists, Oncologists, Surgeons). Physicians will be recruited from country-specific physician databases and ADOReg (ADO, Arbeitsgemeinschaft Dermatologische Onkologie; Reg, Registry).

Selection of patients

In the prospective cohort CSCC patients treated with Cemiplimab and the retrospective cohort patients first diagnosed with advCSCC Jan/2012-Aug/2019 will be selected. These physicians or their assigned staff will be responsible for patient chart identification, qualification and selection, data abstraction, completion of the patient eCRF, resolution of data queries and data validations.

9 CASE REPORT FORM (CRF)

Study data obtained in the course of the study will be recorded on electronic CRFs (eCRF) by trained site personnel. eCRF should be completed for each patient documented in the study. Corrections to the eCRF will be entered in the eCRF by the physician or an authorized designee. All changes, including date, time, and person performing corrections, will be available via the audit trail, which is part of the system. For corrections made via data queries, a reason for any alteration must be provided.

The following data collection forms will be used for the study:

CSCC patient eCRFs will be used to abstract data from patient medical records and will mainly focus on collection of the data on patient and clinical characteristics, treatment patterns, outcomes, and healthcare resource use, and will cover the period from before mCSCC or ladvCSCC diagnosis to most recent follow-up or death, whichever comes later.

PARAMETER AND DEFINITIONS for the CRF's

Outcome(s)	Specific parameter	Definition	Record in Visit (month)
Clinical outcomes	Mortality, all cause, advCSCC related, and date of death	Defined as death due to all cause or disease related	-
	OS from diagnosis	Defined as time from 1st Cemiplimab treatment until death from any cause, censoring for date of most recent follow-up in surviving patients	-
	Progression	Defined as documented in medical records	3,6,9,12,18,24,36
	Date of progression	Defined as date of first documented progression in the medical record	3,6,9,12,18,24,36
	Time to next treatment (TTNT)	Defined as time from start of Cemiplimab treatment to the start of next systemic therapy or death	-
	PFS	Defined as documented start of systemic Cemiplimab therapy until disease progression or death	3,6,9,12,18,24,36
Patient		male / female	Baseline

characteristics	Gender		
	Nationality		Baseline
	Year of birth		Baseline
	Skin phototype	Defined as Type 1, 2…..6	Baseline
	Informed consent		Baseline
	Comorbidities	Auto-immune-disease, hematologic disease, severe cognitive impairment, etc.	Baseline and 3,6,9,12,18,24,and 36
	Quality of life data (QoL)	Questionnaire: EORTC – QoL Core 30	Baseline and 3,6,9,12,18,24,and 36
	Pain	Questionnaire: EORTC – QoL Core 30	Baseline and 3,6,9,12,18,24,and 36
	Adverse events (AE) Quality of life data Reasons for discontinuing therapy Frequency of administration	Defined event as yes/no (specify, related/unrelated to anticancer therapy, serious/non-serious as documented in medical records NOTE: We will limit data collection to Common Terminology Criteria for AE (CTCAE)5.0 as documented in the medical record.Questionnaire: EORTC – QoL Core 30 Defined as lack of response, disease progression, toxicities, side effects, therapy completion, patient decision, death, other (specify) Defined as every day (QD), twice a day (BID), every week (QW), every other week (Q2W), every three weeks (Q3W), every four weeks (Q4W), other	Baseline and 3,6,9,12,18,24,and 36
	Adverse events (AE)	Defined event as yes/no (specify, related/unrelated to anticancer therapy, serious/non-serious as documented in medical records NOTE: We will limit data collection to Common Terminology Criteria for AE (CTCAE) 5..0 as documented in the medical record.	Baseline and 3,6,9,12,18, 24,36
Lab results	Lab parameter LDH		Baseline
Status	Date of physical check-up		Status at Baseline

	Organ transplantation		
	Immunosuppressive therapy		
	Substantial tumor syndromes		
	Specification of substantial tumor syndromes		
	Disease & medication		
Primary diagnosis	Date of diagnosis		All primary diagnosis at Baseline
	Evaluation		
	Tumor status		
	Histological subtype		
	Tumor localization		
	TNM classification		
	Clinical stage		
	ECOG performance status	Defined as 0, 1, 2, 3, 4, measured at advanced diagnosis, at each LOT, prior to and following radiation for early disease, where applicable	
	Infiltration depth and bone involvement		
	Initial treatment of primary tumor		
	Primary surgery	If yes: date, procedure	
	Re-excision	If yes:, date, procedure, micrographic controlled surgery, final resection border, cumulative safty distance (cm)	
	Tumor size of the histo block	horizontial tumor diameter (cm), vertical tumor size (mm), differentiation level	
	High risk factors		
	Further synchronous CSCC		
	Curative surgery of ladvCSCC	Yes or no	
	Tumor board	Yes or no. If yes: decision realized (yes or no)	
	Metastases	Locoal regional or distant	
Recurrence	Date of diagnosis		All recurrence

diagnosis			diagnosis at Baseline
	Evaluation		
	Tumor status		
	Histological subtype		
	Tumor localization		
	TNM classification		
	Clinical stage		
	ECOG performance status	Defined as 0, 1, 2, 3, 4, measured at advanced diagnosis, at each LOT, prior to and following radiation for early disease, where applicable	
	Infiltration depth and bone involvement by local recurrence		
	Initial treatment of primary tumor		
	Primary surgery	If yes: date, procedure	
	Re-excision	If yes: date, procedure, micrographic controlled surgery, final resection border, cumulative safty distance (cm)	
	Tumor size of the histo block	horizontial tumor diameter (cm), vertical tumor size (mm), differentiation level only by local recurrence	
	High risk factors by local recurrence		
	Further synchronous CSCC by local recurrence		
	Curative surgery of ladvCSCC	Yes or no	
	Tumor board	Yes or no. If yes: decision realized (yes or no)	
	Metastases	Locoal regional or distant	
Restaging	Date of diagnosis		All restaging parameters at Baseline
	Evaluation		
	Tumor status		
	Histological subtype		
	Tumor localization		

	TNM classification		
	Clinical stage		
	ECOG performance status	Defined as 0, 1, 2, 3, 4, measured at advanced diagnosis, at each LOT, prior to and following radiation for early disease, where applicable	
	Infiltration depth and bone involvement		
	Differentiation level		
	High risk factors		
	Further synchronous CSCC		
	Response	Yes or no	
	Tumor board	Yes or no. If yes: decision realized (yes or no)	
	Metastases	Locoal regional (type, single or multiple) or distant (localization, single or multiple)	
Surgery	Date of surgery		All at Baseline
	Evaluation		
	Marked lymph nodes (sentinel)	Yes or no	
	Surgery procedure		
	Diameter of largest lymph node	(cm)	
	Capsule break	Yes or no	
	Number of removed lymph nodes		
	Number of lymph nodes with metastases	Maximal size (cm)	
	Completing lymph node dissection	Yes or no If yes: date, procedure, number of dissected lymph nodes, number of lymph nodes with metastases,	
	Residual status		
	Global status of the patient	Tumor free (yes or no)	
Systemic therapy	Intention		All at Baseline
	Line	(1st-line, 2nd-line, …)	

	Regimen		
	Type	(table with medicinal products, table with study medicinal products, table with toxicity)	
	Therapy	From (date) to (date) or ongoing, number of cycles, application,	
	Best response		
	Reason for therapy completion		
	Table with medicinal products	From (date) to (date) or ongoing. Active ingredient / brand name	
	Table with study medicinal products	From (date) to (date) or ongoing. Type, study, study trial	
	Table with toxicity	Date, event term, severity, medical procedure, outcome.	
Locoregional therapy	Date	From (date) to (date)	All locoregional therapy at Baseline
	Medical examination		
	Intention		
	Therapy procedure		
	Residual status	Locoregional efficacy	
	Global status of the patient	Tumor free or do metastases exist at other location?	
Radio Therapy	Date	From (date) to (date)	All radio therapy at Baseline
	Medical examination		
	Intention		
	Organ system		
	Laterality		
	Type		
	Dosage	(Gray)	
	Residual status	Response rate (no, partial, complete)	
	Global status of the patient	do metastases exist at other location?	
Final patient treatment	Date of last visit		Last and final visit at end of follow-up after 36 months

	Reason of last visit		
	Tumor death relation		
	Date of death		

The following table demonstrate a time table for the e-CRF parameter

	Baseline	**Start of Treatment**	**Visits: Month after start of treatment**						
			3	**6**	**9**	**12**	**18**	**24**	**36**
Informed consent	**x**								
Patient characteristics: Gender, age, skin type etc.	**x**								
Medical History									
- General medical history (comorbidities, etc.)	**x**		**x**	**x**	**x**	**x**	**x**	**x**	**x**
- Any prior autoimmune diseases	**x**								
- Tumor related history (primary diagnosis, relapses, treatments, etc.)	**x**		**x**	**x**	**x**	**x**	**x**	**x**	**x**
Current TNM, Grading (at baseline) and R-Situation if indicated	**x**		**x**	**x**	**x**	**x**	**x**	**x**	**x**
QoL (EORTC- QoL Core	**x**		**x**	**x**	**x**	**x**	**x**	**x**	**x**

30)									
Adverse Events			**x**	**x**	**x**	**x**	**x**	**x**	**x**

Study site Questionnaire

As this is a real-world study, the procedures and assessments below are not mandated and do not need to occur at a specific interval. All data deemed pertinent to the management of the patients.

10 TREATMENTS

The purpose of the study is to capture how Cemiplimab is prescribed and managed for patients with advCSCC in a real-world setting, thus compliance to a specific treatment protocol is not applicable.

The prescription of therapies is under the sole responsibility of the treating physician. No investigational agents will be provided to enrolled patients by the sponsor as part of this study.

The patients who will be enrolled in the study will be selected among the patients for whom the physician has decided to prescribe Cemiplimab independently from study entry.

The treating physician should refer to the SmPC for any information on treatment prescribed.

In addition to (or substituting for) Cemiplimab, patients may receive other therapies as deemed necessary by their physicians for the treatment of advCSCC or comorbid conditions. Any concomitant treatment information will be collected throughout the study.

There are no protocol requirements regarding treatment discontinuation. If treatment with Cemiplimab is discontinued permanently or temporarily, patients will remain eligible and will be encouraged to stay in the study.

11 DATA COLLECTION

11.1 DATA COLLECTION

The physicians and/or their assigned staff will be responsible for patient identification, qualification and selection, data abstraction and completion of the patient eCRF. Clinical data will be sourced from patient medical records. Patient data will be de-identified and will be reported in aggregate. eCRFs will be programmed to be available online via encrypted, password protected access. The data entry will be checked for consistency and accuracy.

Following a patient's ICF and enrollment in the study, the frequency with which the patient visits his/her primary CSCC provider will be determined by the local SoC.

11.2 DATA COLLECTED FOR BOTH COHORTS OF THE STUDY

11.2.1 Patient data

Patient and tumor characteristics and treatment patterns

Study data will be collected as described in the table "**PARAMETER AND DEFINITIONS for the CRF's"** (see above).

Response

Best response will be captured as assessed by the study site and may include clinical assessment, radiographic imaging, or symptom resolution. DOR will be defined as time from the time of initial response until documented tumor progression or death.

Study data will be summarized descriptively with consideration for the following:

- Time to next of treatment (TTNT) or death, ORR, Disease Control Rate (DCR), DOR, Time to respond, PFS, OS,
- TTTF including lack of response and discontinuation due to AE
- Incidence and timing of pseudo progression, if applicable
- Response after pseudo progression, if applicable
- Time to response following occurrence of pseudo progression, if applicable
- IrAEs, SAEs

- DSD
- Pain Reduction

12 MANAGEMENT OF DATA

12.1 DATA COLLECTION, VALIDATION AND DATA QUALITY CONTROL AT SANOFI / REGENERON LEVEL

Data will be collected using e-CRF. QoL questionnaires in electronic format (tablet) will be handed out to the patients. Data of the collected QoL questionnaires will be transfered into the data base electronically by Sanofi or a CRO appointed by Sanofi.

The computerized handling of the data by the service provider may generate additional requests to which the participating physician is obliged to respond by confirming or modifying the data questioned.

12.2 MONITORING AND DATA QUALITY CONTROL AT SITE LEVEL

A monitoring will be realized in according to the appropriate SOP. With regard to the quality assurance 5% of the sites will be controlled in view to the quality of data. Every data of a patient will be controlled in the site. Item of the controlling are the informed consent, some specific parameter and the completeness of the SAE reporting.

13 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Procedures for the collection, management and reporting of individual cases of AE/adverse reactions and of any new information that might influence the evaluation of the benefit-risk balance of the product while the observational study is being conducted. Any arrangements made between *Alcedis GmbH* and regulatory authority for the management and reporting of AE/reactions in product observational study should be specified.

If applicable, the exemption process may be followed to define exemptions for the collection of pre-defined AEs which must be described in the protocol and receive Regulatory Authority approval.

All AE regardless of seriousness or relationship to Cemiplimab, spanning from the signature of the ICF form until the end of the study as defined by the protocol (e.g., Long term follow up required by protocol after end of product exposure) for each patient are to be collected by the treating physician and reported to *Alcedis GmbH.* SAE have to be reported within expedited time frame (24 hours of awareness, no later than the following working day), non-serious AE no later than within 30 days of awareness.

Additionally, all AE under any other product of the Sanofi Group must also be reported to PV Sanofi, SAE within 24 hours of awareness, no later than the following working day, non-serious AE no later than within 30 days of awareness.

Furthermore, all AEs generated by the patients QoL questionnaires must be reported to PV Sanofi. These AEs must be entered also in the Sanofi PV database. If patients mention any AE in this QoL questionnaire, the treating physician must document it as a single case and forward it to PV Sanofi.

13.1 SAFETY INSTRUCTIONS

Specific instructions concerning safety management by the treating physician should be developed here, e.g., management of abnormal laboratory values, reporting of outcome events as SAE or not, etc.

All events will be managed and reported in compliance with all applicable regulations.

13.1.1 Definitions of AE and SAE

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with a treatment.

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

- Results in death or;
- Is life-threatening or;
  Note: The term "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.
- Requires inpatient hospitalization or prolongation of existing hospitalization or;
- Results in persistent or significant disability/incapacity or;
- Is a congenital anomaly/birth defect;
- Is a medically important event:

Suspected transmission of infectious agent; is any suspected transmission of an infectious agent via a medicinal product (e.g., product contamination);

- Required Intervention to Prevent Permanent Impairment or Damage (Devices).

If you believe the intervention was necessary to preclude permanent impairment of a body function, or prevent permanent damage to a body structure, either situation suspected to be due to the use of a medical product (This criterion should be added if a specific device is used

Medical and scientific judgment should be exercised in deciding whether expedited 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 intervention to prevent one of the other outcomes listed in the definition above.

13.1.2 Collection of overdose and pregnancy

Overdose: Any case of accidental or intentional overdose, even in the absence of an AE (asymptomatic), is to be reported to PV Sanofi or responsible Vendor (within 24 hours of awareness, no later than the following working day) and recorded accordingly on the corresponding page(s) of in the CRF as explained below. In case of overdose the patient should remain under observation for as long as it is considered appropriate by the treating physician. Appropriate symptomatic measures should be taken.

Pregnancy: Pregnancy occurring in the patient or the female partner of a male patient exposed to a Sanofi drug must be reported to PV Sanofi or responsible Vendor (within 24 hours of awareness, no later than the following working day) and recorded immediately on the corresponding page(s) of in the CRF as explained below.

13.1.3 Obligations of the physician regarding safety reporting

All AE regardless of relationship to Cemiplimab or any other product of the Sanofi group, spanning from the signature of the ICF form until the end of the study as defined by the protocol for each patient, are to be recorded immediately (SAE within 24 hours of awareness, no later than the following working day, non serious AE no later than within 30 d of awareness) for all AEs on the corresponding page(s) of the paper CRF or e-CRF as explained below.

AE reporting to *Alcedis GmbH*

- SAE

In case of paper CRF:

In the case of any AE the treating physician must immediately:

- SEND (within 24 hours, no later than the following working day, preferably by fax) the signed and dated corresponding page(s) in the CRF to *Alcedis GmbH* whose name, address and fax number appear on the third page of this Protocol;
- ATTACH the photocopy of all examinations carried out and the dates on which these examinations were performed. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the study are properly mentioned on any copy of source document provided to *Alcedis GmbH* for laboratory results, include the laboratory normal ranges;

All further documentation should be sent to *Alcedis GmbH* within 24 hours of knowledge, no later than the following working day. In addition, any effort should be made to further document each SAE that is fatal or life threatening within the week (7 days) following initial notification.

In case of e-CRF:

- ENTER (within 24 hours, no later than the following working day) the information related to the AE/SAE in the appropriate screens of the e-CRF; the system will automatically send the notification to the representative of *Alcedis GmbH* after approval of the treating physician within the e-CRF or automatically after a pre-set delay.
- SEND (preferably by e-mail) the photocopy of all examinations carried out and the dates on which these examinations were performed, to *Alcedis GmbH* whose name, email address appear on the first page of this Protocol. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the Study are properly mentioned on any copy of source document provided to *Alcedis GmbH*. For laboratory results, include the laboratory normal ranges
- All further data updates should be recorded in the e-CRF as appropriate, and further documentation as well as additional information (for Lab data, concomitant Medication, patient status ...) should be sent (by e-mail) to *Alcedis GmbH* within 24 hours of knowledge, no later than the following working day, . In addition, any effort should be made to further document each Serious AE

that is fatal or life threatening within the week (7 days) following initial notification.

A back-up plan is used (using paper flow) in case the e-CRF system does not work.

- Non-serious AE

In case of e-CRF:

- ENTER (no later than within 30 days of awareness) the information related to the AE in the appropriate screens of the e-CRF; the system will automatically send the notification to *Alcedis GmbH* after approval of the treating physician within the e-CRF or automatically after a pre-set delay.

In case of paper CRF:

- SEND (no later than within 30 days of awareness) the signed and dated corresponding page(s) in the CRF to *Alcedis GmbH* representative whose name, address appear on the second page of this protocol.

13.2 SAFETY OBSERVATIONS

- The treating physician should take all appropriate measures to ensure the safety of the patients as per normal practice.
- In case of any AE, the patient must be followed up until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized. This may imply that follow-up will continue after the patient has left the study.
- In case of any AE brought to the attention of the treating physician at any time after cessation of Cemiplimab, and considered by him/her to be caused by Cemiplimab with a reasonable possibility, this should be reported to the *Alcedis GmbH*.

13.3 AE OF SPECIAL INTEREST (AESI)

An AE of special interest (serious or non-serious) is one of scientific and medical concern specific to the product or program, for which ongoing monitoring and rapid communication by the treating physician to *Alcedis GmbH* is required. Such AE normally require thorough documentation and investigation to characterize them.

In the event of an AESI, *Alcedis GmbH* will be informed immediately (i.e., within 24 hours, no later than the following working day) even not fulfilling a seriousness criterion, using the specific AESI form as appropriate.

The protocol defines a specific subset of AESIs and laboratory abnormalities that must be immediately reported, even if not fulfilling seriousness criteria. The following events

must be systematically reported by the treating physician as AESIs with immediate notification for all studies:

- Immune related reactions (ir-ARs) including immune-related pneumonitis, colitis, hepatitis, endocrinopathies, immune-related skin adverse reactions, nephritis, and irARs in other organs.
    - *Since Clinical manifestations of irARs are generally autoimmune-like, any AEs considered as irARs with no clear alternative etiology will need to be reported.*

***Note:* for each immune related reaction the Targeted follow-up form has to be fulfilled in addition to the standard AE form.**

- Infusion related reactions (IRRs)
    - *Cases with AEs coded to infusion related reaction, hypersensitivity, type hypersensitivity, drug hypersensitivity and severe or life-threatening infusion- related reactions, including bronchospasm, anaphylaxis, anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, anaphylactoid shock, angioedema, and severe hypotension, during or immediately following the initial infusion, need to be reported.*

***Note:* for each infusion related reaction the Targeted follow-up form has to be fulfilled in addition to the standard AE form.**

- Pregnancy of female subject entered in a study (as well as pregnancy occurring in a female partner of a male subject entered in a study with Sanofi product;
- Pregnancy of a female exposed to a Sanofi product (as well as pregnancy occurring in a female partner of a male exposed to a Sanofi product) will be reported to the CRO *Alcedis GmbH*. It will be qualified as a SAE (only if it fulfills one of the seriousness criteria).

A pregnancy data collection form will be provided to the treating physician to ensure collection of additional information regarding the outcome of the pregnancy. If the exposed female refuses to provide any information regarding the pregnancy and its outcome, this information will be captured on the Sanofi Pregnancy/Drug Exposure via pregnancy data collection form.

- Symptomatic overdose (serious or non-serious) with Sanofi product (overdose of the studied product(s) to be defined here.)

13.4 OBLIGATIONS OF *ALCEDIS GMBH*

During the course of the study, the *Alcedis GmbH* will report to the appropriate Health Authorities and IECs/IRBs all cases that meet expedited reporting criteria in accordance with all local and global regulations

The Sponsor will report all safety observations made during the conduct of the study in the study report.

14 STATISTICAL CONSIDERATIONS

14.1 DETERMINATION OF SAMPLE SIZE

Sample size justification

The primary objective of the study is to describe TTNT or death in patients with advCSCC initially treated with Cemiplimab (prospective cohort) or other therapeutic approaches (retrospective cohort). The sample size is justified based on the precision (half-length of 95%-CI) of median TTNT. Based on the results presented for TTNT in (Ludwig et al, 2015) it is expected, that with 200 patients median TTNT can be estimated with a precision of 10%.

14.2 ANALYSIS POPULATION

All eligible patients will be analyzed

14.3 STATISTICAL METHODS

14.3.1 Analyses variables

14.3.1.1 Primary variable

The TTNT defined as time from start of Cemiplimab treatment to the start of next systemic therapy or death outside BSC. All next systemic treatments excluding BSC will be evaluated.

14.3.1.2 Secondary variables of the prospective cohort

* DOR , DCR (CR+PR+SD) at 3, 6, 9, 12, 18, 24, 36 months
* Patient experience, functional status, QoL and pain, in a real-world setting for patients with advCSCC at 3, 6, 9, 12, 18, 24 and 36 months
* Safety data on study participants defind on paragraph 13
* Characteristics of patients who receive Cemiplimab as treatment for advCSCC in a real-world setting
* OS defined as duration from current mCSCC or ladvCSCC diagnosis and also from the initiation of each LOT until death or end of follow up
* Proportion of patients surviving at month 3, 6, 9, 12, 18, 24 and up to months 36 from initiation of systemic therapy

* PFS defined as time from first documented systemic cemiplimab therapy initiation until progression or treatment discontinuation due death or end of follow up
* Patient demographics and baseline characteristics (incl. age, performance status etc.) at study entry
* Characterization of Cemiplimab usage patterns
* Cemiplimab treatment regimen (initial dose and date of initiation and regimen changes)
* Treatment prior to and post Cemiplimab treatment, incl. surgery, radiation, systemic therapies incl. agents administered, dose, frequency and duration
* Surgery post initiation of Cemiplimab treatment
* DOT
* TNM stage (AJCC or UICC)
* Observed rates, reasons and timing of the discontinuation of Cemiplimab
* TTTF including lack of response and discontinuation due to AE
* Change in patient reported QoL as per EORTC-QLQ-C30 QoL questionnaire during treatment with Cemiplimab (for prospective cohort only)

14.3.1.3 Secondary variables of the retrospective cohort

* Characteristics of retrospective patient population, patterns of care and effectiveness of different treatment options used under routine conditions for advanced CSCC prior to Cemiplimab launch

* Safety data on study participants
* Proportion of patients surviving at month 3, 6, 9, 12, 18, 24 and up to months 36 from initiation of systemic therapy
* PFS defined as time from first documented systemic therapy initiation until progression or treatment discontinuation due death or end of follow up
* Patient demographics and baseline characteristics (incl. age, performance status etc.) at study entry
* TNM stage (AJCC or UICC)
* Patterns of treatment for the retrospective cohort.

14.3.2 Statistical analyses

14.3.2.1 Primary analysis

The primary analysis is descriptive. TTNT will be estimated and visualized for each cohort separately by Kaplan-Meier estimators. Median TTNT will be presented with 95%-confidence intervals. Potential predictors of TTNT will be analyzed using Cox proportional hazards regression.

14.3.2.2 Secondary analysis

All secondary outcomes will be analyzed descriptively.

The rate of ORR and 95%-confidence interval will be given for each cohort. In addition and in an exploratory way, the pooled rate and its 95%-confidence interval will also be given. Potential predictors of response will be analyzed using logistic regression and/or Factorial Multiple Correspondences Analyses.

For time to event parameters, Kaplan-Meier curves will be presented and median time to event will be estimated with corresponding 95%-confidence intervals.

14.4 INTERIM ANALYSIS

It is planned to perform yearly interim analyses in addition to a final report at the end of the study.

15 TASK AND RESPONSIBILITIES

15.1 RESPONSIBILITIES OF STUDY COMMITTEES

The non-interventional study consist of the study committee and scientific director. The research director and the study committee advises the sponsor on the planning and performance of the project as well as the preparation of the publication(s) after the results become available.

15.2 RESPONSIBILITIES OF THE STUDY SITE(S)

The study site will perform the study in accordance with this protocol, applicable local regulations and international guidelines.

It is the physicians' responsibility to:

- Obtain any required local or institutional administrative or ethics approval prior to initiating data collection
- Complete the eCRF and record all data pertinent to the study. She/he will ensure that the information reported in the CRF is precise and accurate
- Make data available for quality audits and respond to data queries on a timely basis

15.3 RESPONSIBILITIES OF SANOFI

Sanofi is responsible for taking all reasonable steps and providing adequate resources to ensure the proper conduct of the study. Sanofi and Regeneron are responsible for reviewing and approving this protocol.

16 ETHICAL AND REGULATORY STANDARDS

16.1 ETHICAL PRINCIPLES

Prior to launching data collection, depending upon local regulations, country specific regulatory authority and/or Independent EC review and approval will be obtained by Sponsor or Delegate, participating physician if applicable by local regulation

16.2 LAWS AND REGULATIONS

This study will be conducted in accordance with the guidelines for Good Epidemiology Practice. Each participating study site should locally ensure all necessary regulatory submissions (e.g.: IRB/IEC) are performed in accordance with local regulations including local data protection regulations.

Premature Termination of the study

The sponsor has the right to terminate the study prematurely. Should the sponsor decide to terminate the study, the study site(s) will be notified in writing.

Close-out of a site

The sponsor and the study site have the right to close-out a site prematurely.

Physicians Decision

The physician must notify the sponsor of a desire to close-out a site in writing, providing at least 30 days' notice. The final decision should be made through mutual agreement with the sponsor. Both parties will arrange the close-out procedures after review and consultation.

Sponsor's Decision

The sponsor will notify the study site(s) of a decision to close-out a study site in writing. Reasons may include the following, among others:

- The study site has received all items and information necessary to perform the study, but has not enrolled any patient within a reasonable period of time
- The study site has violated any fundamental obligation in the study agreement, including but not limited to, breach of the applicable laws and regulations,
- The total number of patients required for the study is enrolled earlier than expected

In all cases, the appropriate IRB/EC and Health Authorities must be informed according to applicable regulatory requirements, and adequate consideration must be given to the protection of the patients' interests.

17 ADMINISTRATIVE EXPECTATIONS

17.1 RECORD RETENTION IN STUDY SITES

The study site must retain all essential study documents, including ICFs, source documents, copies of CRFs for at least 25 years following the completion or discontinuation of the study, or longer if a longer period is required by relevant regulatory authorities.

It is recommended that the study site retains any study documents after the completion or discontinuation of the study, unless otherwise specified in additional standards and/or local laws. However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

17.2 CONFIDENTIALITY

All material, information (oral or written) and unpublished documentation provided to the study site (or any action carried out by Sanofi and Regeneron on their behalf), including the present protocol and the eCRF, are exclusive property of Sanofi and Regeneron.

These materials or information (both global and partial) cannot be given or disclosed by the physician(s) or by any person of her/his group to unauthorized persons without the prior formal written consent of Sanofi and Regeneron.

The physician shall consider as confidential all the information received, acquired or deduced during the study and will take all necessary steps to ensure that there is no break of confidentiality, other than for information to be disclosed by law.

17.3 DATA PROTECTION

The study site must take all appropriate measures to ensure that the anonymity of each study patient will be maintained. Patients should be identified by patient identification number, only, on eCRFs or other documents submitted to the sponsor. Documents that will not be submitted to the sponsor (e.g., signed ICF) must be kept in strict confidence.

The patient's and study site personal data, which may be included in the sponsor database, will be treated in compliance with all applicable laws and regulations. The sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

No personally identifiable data will be included in Sanofi and Regeneron’s database, nor its designee. All data shall be treated in compliance with all local applicable laws and regulations. When archiving or processing personal data pertaining to the study site

and/or to the patients, Sanofi and Regeneron and its designee shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

17.4 SANOFI AND REGENERON AUDITS BY REGULATORY AGENCIES

Due to the nature of this study, audits are unlikely. However, in the event of any audit by a competent authority, the study site agrees to allow authorities to have direct access to his/her study records for review, being understood that these personnel are bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The study site will make every effort to help with the performance of the audits giving access to all necessary facilities, data, and documents.

This study may be subject to a quality assurance audit by the sponsor or regulatory authorities. Should this occur, the physician is responsible for:

- Providing access to all necessary facilities, study data, and documents for the audit
- Taking all appropriate measures requested by the sponsor to resolve the problems found during the audit

Documents subject to audit include but are not limited to all source documents, CRFs, medical records, correspondence, ICFs, institutional review board (IRB)/ EC files, In addition, representatives of the sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the study site(s) institution.

In all instances, the confidentiality of the data must be respected.

17.5 PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

Sanofi and Regeneron can decide at any time and for any reason to prematurely stop or to interrupt the study; the decision will be communicated by MDA in writing to the study site.

Similarly, should the study site decide to withdraw from the study, she/he will have to immediately inform MDA in writing.

If appropriate, according to local regulations, Ethic Committee(s) (IRB/IEC) and Competent Authorities should be informed.

17.6 OWNERSHIP AND USE OF DATA AND STUDY RESULTS

No use of the data will be possible without the authorization of Sanofi and Regeneron.

Sanofi and Regeneron will have full access to the final de-identified data allowing for appropriate academic analysis and reporting of the study results.

17.7 PUBLICATIONS

Sanofi / Regeneron are responsible for presentations and/or publications. The study results must be submitted for review by Sanofi/Regeneron before publication.

All study sites give full authority to the Sanofi/Regeneron for primary presentation and/or primary publication of results. No other publication is allowed before the primary publication. Any subsequent presentation or publication by a study participant (including for substudies) must be approved by Sanofi/Regeneron and make reference to the study and the primary publication.

The final decision to publish any manuscript/ abstract/ presentation will be made by Sanofi and Regeneron allowing for internal review and comments.

All manuscript/ abstract/ presentation must be submitted to the internal review of Sanofi and Regeneron at least forty-five (45) calendar days in advance of submission, unless a previously agreed upon timeline is available. Sanofi and Regeneron may request that its name and/or names of one or several of its employees appear or do not appear in such publication, except where study funding disclosures are required by journal policy.

Sanofi and Regeneron can delay publication or communication for a limited time in order to protect the confidentiality or proprietary nature of any information contained therein.

AUTHORSHIP CRITERIA

Physicians from each country may be considered for authorship on manuscripts ensuing from this study. Authorship will be considered based upon physicians
1) meeting International Committee of Medical Journal Editors (ICMJE) guidelines, and
2) based upon volume of patient enrollment within each country. ICMJE guidelines require:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

18 STUDY PROTOCOL AMENDMENTS

Any change to the protocol will be recorded in a written amendment, which will be signed by the physician. Amendment to the protocol may require regulatory submissions (e.g., IRB/IEC) in accordance with local country regulations.

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APPENDIX 1: PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes Table for the current amendment is located before the Table of Contents (TOC).

Amended Observational Protocol Version 2.0: (29-Oct-2021)

This amended observational protocol (V2.0) is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it does not significantly impact the safety or physical/mental integrity of participants, nor the scientific value of the study.

Overall Rationale for the Amendment

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Names & Addresses of Study Management	[redacted]	New address as of mid of December 2021
Names & Addresses of Study Management	Global statistician changed to the local statistician	Global Statistician no longer available
Names & Addresses of Country Teams representative	[redacted]: Change of clinic address	[redacted] has been working at the Johannes Wesling Klinikum Minden since 01.04.21
Names & Addresses of Country Teams representative	Instead of [redacted] is Country Team Representative in Switzerland	New Country Team Representative in Switzerland
Names & Addresses of Scientific Director	[redacted]: Change of clinic address	[redacted] has been working at the Johannes Wesling Klinikum Minden since 01.04.21
Names & Addresses of Sponsor	Sanofi-Aventis GmbH, Österreich: Twin Tower A, 29. Stock, Wienerbergstr. 11, A-1100 Wien	Clarification of the name of the sponsor and new address as of 01.12 2021
1 Synopsis Scientific Committee Chair Person	Instead of [redacted] is Scientific Committee Chair Person in Switzerland	New Scientific Committee Chair Person in Switzerland
1 Synopsis Study Design and Duration	"Sanofi-ICF" is used instead of "ICF"	Clarification that the Sanofi-ICF is only required for the prospective cohort
1 Synopsis Study Population Inclusion criteria	Retrospective Cohort: no Sanofi-ICF is needed	Clarification that the Sanofi-ICF is not required for the retrospective cohort
1 Synopsis Study Population Inclusion criteria	Retrospective Cohort: including patients who are no longer alive	Clarification that it is planned to include patients in retrospective cohort who are no longer alive
1 Synopsis	Retrospective Cohort: no Sanofi-ICF is needed	Clarification that the Sanofi-ICF is not required

Main Data Collected retrospective cohort		for the retrospective cohort
1 Synopsis Main Data Collected retrospective cohort	Retrospective Cohort: including patients who are no longer alive	Clarification that it is planned to include patients in retrospective cohort who are no longer alive
1 Synopsis Estimated Duration of the Study	FPI changed to 01.03.21, LPI changed to 01.03.23, LPO changed to 01.03.26	Adjustment of data after delayed enrollment of the 1st patient in Germany
7.2 Study Duration and Dates	FPI (start of documentation) changed to 01.03.21, LPI changed to 01.03.23, LPO (end of documentation) changed to 01.03.26, Data base lock changed to 01.05.26, estimated clinical study report changed to 01.01.27	Adjustment of data after delayed enrollment of the 1st patient in Germany
8.2 Selection of patients – Inclusion criteria	Retrospective cohort: Change of > 18 years to ≥ 18 years and including patients who are no longer alive	Correction and Clarification
8.3 Selection of patients – Exclusion criteria	Retrospective cohort: advCSCC of unknown primary origin	Inserting a missing paragraph
8.3 Selection of patients - Premature withdrawal from the study	no Sanofi-ICF is needed	Clarification that the Sanofi-ICF is not required for the retrospective cohort
9 Case Report Form (CRF) Definitions for the CRF – Clinical Outcomes	TTNT: Change from "start of next medication" to "start of next systemic therapy"	Clarification
13 Management and reporting of adverse events/adverse reactions	“Alcedis” instead of “Aldedis”	Correction of a spelling mistake
13.3 AE of special interest (AESI)	“CRO” instead of “r”	Correction of a spelling mistake
14.3.1.1 primary variable	All next treatments excluding BSC will be evaluated. Change from "start of next medication" to "start of next systemic therapy”	Insertion of the sentence for further explanation Clarification