Universitätsklinikum Erlangen

Randomized phase II study of immune stimulation with Pembrolizumab and radiotherapy in second line therapy of metastatic head and neck squamous cell carcinoma (IMPORTANCE)

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Statistical Analysis Plan

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List of abbreviations

AE	Adverse event
CI	Confidence Interval
CR	Complete Response
CRF	Case report form
CTC	Common Terminology Criteria
CTCAE	Common terminology criteria for adverse events
df	derived from
DOR	duration of response
eCRF	Electronic Case Report Form
EORTC	European Organisation on Research and Treatment of Cancer
F	Full analysis set
HR	Hazard ratio
ICH	International conference on harmonization of technical requirements for registration of pharmaceuticals
ITT	Intention to treat
LKP	Clinical Trial Director / Principal Investigator according to AMG (Leiter der Klinischen Prüfung)
NCI	National Cancer Institute
N.A.	Not applicable
ORR	Overall Response Rate
OS	Overall survival
PAM	Pre-analysis Meeting
PD	Progressive Disease
PD-L1	Programmed Cell Death Receptor Ligand 1
PFS	Progression-free survival
PP	Per protocol (set)
PR	Partial Response
QLQ	Quality of life questionnaire
RECIST, iRECIST	(immune) Response Evaluation Criteria In Solid Tumors
RR	Response rate
S	Safety analysis (set)
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable Disease
SD	Standard deviation
SOP	Standard Operating Procedure
SQL	Standard Query Language
VAS	Visual analogue scale

Short codes for data tables are provided in Appendix 1.

1. INTRODUCTION

This statistical analysis plan (SAP) is based on the study protocol V. 1.6 dating from 20-02-2023. It specifies the analytical procedures to be performed at the planned final analysis. It focuses on the clinical parameters of the study. The translational research program is not included, as it is to be handled separately and described in separate documents (except for the analysis of prognostic/predictive impact of potential biomarkers [PD-L1] on the primary efficacy endpoint).

All analyses of this phase II trial are performed giving results for the two randomisation arms separately, and for the total group.

Methodologically, the analysis will follow the outlines of the protocol, and the ICH Guideline E9 "Statistical principles for clinical trials". The scope and contents of the SAP are primarily described in the sections 3.0 (Objectives & Hypotheses) and 8.0 (Statistical Aspects) of the protocol.

Throughout this document and the analysis reports, the randomized treatment groups are referred to as "arm A" (experimental arm, pembrolizumab and radiotherapy), and "arm B" (control arm, pembrolizumab), as defined in the protocol.

The analysis report(s) will be written in English language in MS WORD format. Figures will be produced and delivered in MS POWERPOINT format in order to facilitate their use in presentations or publications.

Amendments to this SAP may be required during the course of the study, but should be finalized after the pre-analysis meeting (PAM) and before embarking on the analysis of any efficacy objectives.

2. DEFINITION OF ANALYSIS SETS

The following data sets for analysis are defined based on the initial enrolment and randomization procedures, the fulfilment of selection criteria, the minimum amount of treatment received and the amount of available information for the respective patient. Every patient will be analysed according to his/her randomization assignment.

Patient unequivocally not fulfilling the selection criteria according to their known status at the time point of enrolment will be excluded from all statistical analyses. These "non-eligible" cases will be discussed and defined prospectively during the pre-analysis meeting, in a blinded fashion, if possible. A short case report will be provided for each of these patients.

Analysis of demographic and anamnestic baseline characteristics

These analyses are performed on all enrolled, eligible patients (full analysis set for these variables).

Full Analysis Set (F) / Intention-to-treat population for all other analyses

The full analysis set (F), based on the intent-to-treat (ITT) population, will consist of all patients who were registered *and randomized* to this study. The patients will be evaluated in the arm to which they were randomized, independent of whether and which medication they received. The ITT population is the prevailing population for the evaluation of all efficacy parameters.

Per-Protocol Analysis Set (PP)

This set contains all eligible patients having completed radiotherapy (arm A) and at least two cycles of pembrolizumab according to the protocol. Only the primary endpoint and the PFS analysis is repeated on the per-protocol analysis set as a sensitivity analysis.

Safety Analysis Set (S)

The evaluation of tolerability is carried out based on the safety population. This includes all randomized patients who received at least one dose of study therapy according to the protocol.

3. ANALYSIS PROGRAM

3.1 Primary study endpoint

The present trial is designed as a randomized phase II study which aims at estimating a superior therapeutic efficacy of the experimental regimen, pembrolizumab combined with local radiotherapy (arm A), in relation to the standard treatment consisting of pembrolizumab only (arm B). Accordingly, the research hypothesis of the study is one-sided. The overall response rate (ORR), i.e., achieving CR or PR as best response during/after treatment, according to iRECIST, is chosen as primary efficacy endpoint. The calculation is based on the total number of patients of the ITT population as denominator in the primary analysis (and with the number of patients of the PP population as denominator in the per-protocol analysis).

A p value resulting from a one-sided Fisher's exact test comparing the study arms is calculated, with $p \leq 0.1$ defined as significant. The risk difference (RD) and the odds ratio (OR) will be calculated, the latter with exact two-sided 95%, 90%, and 80% confidence intervals, with the lower boundary of the 80% confidence interval corresponding to the primary study hypothesis. In addition to the crude comparison, a multivariable analysis including the stratification factors at randomisation (ECOG 0/1; presence/absence of distant metastases) is performed.

3.2 Secondary study endpoints

Response rate according to RECIST will be analyzed similarly to the primary endpoint. Metric changes in (non-irradiated) target lesions will be described with mean, median, interquartile range, and range, and may be compared using the Wilcoxon rank sum test.

PFS, OS, and duration of response (DOR, defined as PFS in the subgroup of patients achieving iRECIST-defined CR or PR) will be estimated by the product limit method of Kaplan and Meier, providing the numbers of events and censored cases, with survival curves exploratively compared between the arms using the logrank test as well as the correspondingly calculated hazard ratio with confidence interval (from a univariate Cox model). The period for calculation of PFS begins with the date of randomization and ends with the reported date of either RECIST-based PD, or death (for whatever reason), or the final date of the patient being recorded as free of progression during the follow-up period (censored cases). For comparison, a second version of the PFS analysis will be based on iRECIST PD, with the RECIST-based PD considered only, if an iRECIST-based restaging is not recorded. The period for calculation of OS begins with the date of randomization and ends with the reported date of death (for whatever reason), or the final date of the patient being recorded as alive during the follow-up period (censored cases). In addition, major

protocol violations, e.g. unauthorized tumor treatment before progression, may lead to censoring at the time point of this event (cf. section 5).

Toxicity rates based on CTCAE categories and severity grades are analysed descriptively and may be compared by Fisher´s exact test, χ^2 test or Mantel-Haenszel test (or trend test according to Cochran/Armitage), respectively, in case of major differences, namely with respect to the proportions of patient experiencing any toxicity of grade 3 or higher.

A subgroup analysis on the prognostic/predictive effect of PD-L1 on ORR according to iRECIST is prospectively planned, but outside the scope of this SAP.

3.3 General statistical methods and data presentation

Except for the primary endpoint, as described above, all parameters will be evaluated in an explorative or descriptive manner, providing means, medians, interquartile and total ranges, standard deviations, counts and proportions, or Kaplan-Meier curves, as appropriate for the respective data types.

In general, all analyses will be presented and calculations performed on the basis of the data actually available for each item (observed case analyses). Incomplete time-to-event observations will be handled as censored measurements.

If exploratory p values for differences between randomisation-defined arms or (sub)groups (e.g. prognostic) are calculated for selected items, they will be presented explicitly without referring to pre-specified hypotheses or a significance level. Usually, no error adjustment for multiple testing will be performed. Thus, the p values will reflect the comparison-wise error and not the experiment-wise error. All explorative p values will be two-sided, if not defined otherwise. The statistical methods described in this section are suited for the data and distributions usually expected in this type of trials.

3.4 Detailed analysis procedures

A description of the analyses to be performed is provided in the following tables. The contents of the final study report will correspond to this structure. The short names identifying the eCRF page (and the respective database table) refer to the Secutrial form description after the uniform header “mnpimp…” or “empimpr_…”, as provided in the files Dossier.pdf and Datensatztabelle_IMP_Dev_22_20250115-102341.xlsx. Names of data columns are written in CAPITAL LETTERS .

PARAMETER / ANALYSIS DESCRIPTION	CRF PAGE*	ANALY-SIS SET	METHODS	COMM.
GENERAL				
• Description of study/analysis population and evaluability with respect to eligibility, available forms and information throughout the course of protocol therapy (corresponding to a CONSORT diagram), by randomized treatment group				based on information from monitoring, PAM and database
• Definition/identification of F, PP and S analysis sets				
• Violation of inclusion/exclusion criteria and other protocol violations leading to exclusion in primary endpoint analysis, or, in addition, censoring in long-term efficacy endpoints				list provided by monitoring / data management (for PAM)
• Creation of files representing the study/analysis populations			SQL	
• Course of recruitment		F	figure	by date of enrolment, provided by study centre if available
• Distribution by centre		F	DA	provided by study centre if available
• Randomisation arm allocation	RAN	F	DA	RANDOMISATION
• Stratification factors (M0/M1; ECOG 0/1)	RAN	F	DA	ECOG, PAT_GRUPPE

df = derived from; F = full analysis set; PP = per protocol set; S = safety analysis set; SQL = Standard Query Language; DA = descriptive analysis; HIS = histogram; T = Significance test; * according to eCRF description ([e]mnpimp…) and appendix 1.

PARAMETER / ANALYSIS DESCRIPTION	**CRF PAGE***	**ANALYSIS SET**	**METHODS**	**COMM.**
DEMOGRAPHIC DATA				
• Age at randomisation	INF, RAN	F	DA, HIS	(DAT_RANDOM - 01.[GEB_DAT])/ 365.25
• Gender	INF	F	DA	

df = derived from; F = full analysis set; PP = per protocol set; S = safety analysis set; SQL = Standard Query Language; DA = descriptive analysis; HIS = histogram; T = Significance test; * according to eCRF description ([e]mnpimp…) and appendix 1.

PARAMETER / ANALYSIS DESCRIPTION	**CRF PAGE***	**ANALYSIS SET**	**METHODS**	**COMM.**
BASELINE, TUMOR DATA AT INITIAL DIAGNOSIS				
• Time since initial diagnosis	RAN, PT	F	DA	DAT_RANDOM – PT_DAT
• Primary tumor localization: Oral cavity	PT	F	DA	
• Primary tumor localization: Oropharynx	PT	F	DA	
• Primary tumor localization: Hypopharynx	PT	F	DA	
• Primary tumor localization: Larynx	PT	F	DA	
• Primary tumor localization: Nasopharynx	PT	F	DA	
• Primary tumor localization: CUP (cancer of unknown origin)	PT	F	DA	
• p16 status	PT	F	DA	
• T stage	PT	F	DA	Derived from PT_T and PT_ABC
• N stage	PT	F	DA	
• M stage	PT	F	DA	
• Localisation of metastases - Lung	PT	F	DA	
• Localisation of metastases - Liver	PT	F	DA	
• Localisation of metastases - CNS	PT	F	DA	
• Localisation of metastases - Skin	PT	F	DA	
• Localisation of metastases - Other	PT	F	DA	
• L category	PT	F	DA	
• V category	PT	F	DA	
• Grading	PT	F	DA	
• R category	PT	F	DA	

df = derived from; F = full analysis set; PP = per protocol set; S = safety analysis set; SQL = Standard Query Language; DA = descriptive analysis; HIS = histogram; T = Significance test; * according to eCRF description ([e]mnpimp…) and appendix 1.

PARAMETER / ANALYSIS DESCRIPTION	CRF PAGE*	ANALYSIS SET	METHODS	COMM.
BASELINE, TUMOR STATUS AT STUDY ENTRY				
• Relapse present?, y/n	REZ	F	DA	KEIN_REZ
• Study treatment performed at local relapse, y/n	REZ	F	DA	THERAPIE_REZ
• T stage	REZ	F	DA	Derived from REZ_T and REZ_ABC
• N stage	REZ	F	DA	
• M stage	REZ	F	DA	
• L category	REZ	F	DA	
• V category	REZ	F	DA	
• Grading	REZ	F	DA	
• R category	REZ	F	DA	
• Distant metastases present?, y/n	FM	F	DA	KEINE_FM
• Localisation of metastases - Lung	FM	F	DA	
• Localisation of metastases - Liver	FM	F	DA	
• Localisation of metastases - CNS	FM	F	DA	
• Localisation of metastases - Skin	FM	F	DA	
• Localisation of metastases - Other	FM	F	DA	

df = derived from; F = full analysis set; PP = per protocol set; S = safety analysis set; SQL = Standard Query Language; DA = descriptive analysis; HIS = histogram; T = Significance test; * according to eCRF description ([e]mnpimp…) and appendix 1.

PARAMETER / ANALYSIS DESCRIPTION	CRF PAGE*	ANALYSIS SET	METHODS	COMM.
TUMOR PRE-TREATMENT				
• No previous treatment, y/n	RKT	F	DA	KEINE_VORTHERAPIE
• Tumor surgery, y/n	RKT	F	DA	
• Chemotherapy, y/n	RKT	F	DA	
• Radiotherapy, y/n	RKT	F	DA	
• Other, y/n	RKT	F	DA	
OTHER BASELINE CHARACTERISTICS				
• Smoker status	RKT	F	DA	RAUCHERSTATUS
• Clinically relevant concomitant disease(s)?, y/n	RKT	F	DA	ERKRANKUNG_JA_NEIN
• Performance status, at recruitment	KUSC	F	DA	ECOG

df = derived from; F = full analysis set; PP = per protocol set; S = safety analysis set; SQL = Standard Query Language; DA = descriptive analysis; HIS = histogram; T = Significance test; * according to eCRF description ([e]mnpimp…) and appendix 1.

PARAMETER / ANALYSIS DESCRIPTION	**CRF PAGE***	**ANALYSIS SET**	**METHODS**	**COMM.**
PROTOCOL THERAPY				
• Arm A: radiotherapy applied? y/n	RAD	F	DA	RAD_J_N
• Arm A: duration of radiotherapy	RAD	F	DA	RT_ENDE – RT_BEGINN
• Arm A: number of fractions	RAD	F	DA	ANZ_ FRAKTIONEN
• Arm A: total dose GTV	RAD	F	DA	GD_GTV
• Arm A: total dose according to protocol? y/n	RAD	F	DA	DOSIS_NACH_ PLAN
• Arm A: premature termination of radiotherapy? y/n	RAD	F	DA	RT_ABBRUCH
• No. of pembrolizumab cycles	EOT	F	DA	PEMBRO_ GESAMT
• Duration of pembrolizumab treatment [weeks]	PEM	F	DA	DAT_GEGEBEN latest – earliest date + 3 weeks
• Number of cycles with delayed application	PEM	F	DA	NACH_ PROTOKOLL
• Number of patients with at least one delayed application	PEM	F	DA	NACH_ PROTOKOLL

df = derived from; F = full analysis set; PP = per protocol set; S = safety analysis set; SQL = Standard Query Language; DA = descriptive analysis; HIS = histogram; T = Significance test; * according to eCRF description ([e]mnpimp…) and appendix 1.

PARAMETER / ANALYSIS DESCRIPTION	**CRF PAGE***	**ANALYSIS SET**	**METHODS**	**COMM.**
END OF PROTOCOL TREATMENT				
• Regular end of protocol treatment after 2 cycles, y/n	EOT	F	DA	ENDE_ BEHANDLUNG
• Regular end of protocol treatment after 12 months, y/n	EOT	F	DA	ENDE_ BEHANDLUNG
• Reason for the premature end of protocol treatment	EOT	F	DA	ENDE_ BEHANDLUNG

df = derived from; F = full analysis set; PP = per protocol set; S = safety analysis set; SQL = Standard Query Language; DA = descriptive analysis; HIS = histogram; T = Significance test; * according to eCRF description ([e]mnpimp…) and appendix 1.

PARAMETER / ANALYSIS DESCRIPTION	CRF PAGE*	ANALYSIS SET	METHODS	COMM.
EFFICACY, RESPONSE ACCORDING TO IRECIST				
• Response (all response categories) at first restaging, non-irradiated lesions, based on iRECIST	IREC	F	DA	IRECIST_NICHT_RT
• Response (all response categories) at first restaging, irradiated lesions, based on iRECIST (arm A only)	IREC	F	DA	IRECIST_RT
• Objective response (CR + PR) at first restaging, non-irradiated lesions, based on iRECIST	IREC	F	DA, T	IRECIST_NICHT_RT; Fisher's exact test
• Objective response (CR + PR) at first restaging, irradiated lesions, based on iRECIST (arm A only)	IREC	F	DA	IRECIST_RT
• Best overall response (all response categories), non-irradiated lesions, based on iRECIST	IREC, EREC	F, PP	DA, T	IRECIST_NICHT_RT, df lowest value achieved; trend test
• Best overall response (all response categories), irradiated lesions, based on iRECIST (arm A only)	IREC, EREC	F	DA	IRECIST_RT, df lowest value achieved
• Overall objective response (CR + PR), non-irradiated lesions, based on iRECIST **(primary endpoint)** Cf. section 3.1, 3.3 for further details	IREC, EREC	F, PP	DA, T	IRECIST_NICHT_RT, df lowest value achieved; Fisher's exact test; multivariable analysis including stratification factors
• Overall objective response (CR + PR), irradiated lesions, based on iRECIST (arm A only)	IREC, EREC	F	DA	IRECIST_RT, df lowest value achieved
• Sum of diameters of iRECIST-defined, non-irradiated lesions at the various (re)staging visits	IREC, EREC	F	DA, Figure	Figure with means and SD, for arm A and B

df = derived from; F = full analysis set; PP = per protocol set; S = safety analysis set; SQL = Standard Query Language; DA = descriptive analysis; HIS = histogram; T = Significance test; * according to eCRF description ([e]mnpimp…) and appendix 1.

PARAMETER / ANALYSIS DESCRIPTION	CRF PAGE*	ANALYSIS SET	METHODS	COMM.
EFFICACY, RESPONSE ACCORDING TO RECIST				
• Best overall response (all response categories), non-irradiated lesions, based on RECIST	IREC, EREC	F	DA	RECIST_NICHT_RT, df lowest value achieved
• Best overall response (all response categories), irradiated lesions, based on RECIST (arm A only)	IREC, EREC	F	DA	RECIST_RT, df lowest value achieved
• Overall objective response (CR + PR), non-irradiated lesions, based on RECIST	IREC, EREC	F	DA,T	RECIST_NICHT_RT, df lowest value achieved; Fisher's exact test
• Overall objective response (CR + PR), irradiated lesions, based on RECIST (arm A only)	IREC, EREC	F	DA	RECIST_RT, df lowest value achieved
EFFICACY, PFS				
• Progression-free survival from randomization, Kaplan-Meier estimation providing number of patients at risk (Date of restaging to be retrieved from CTMR, identified by MNPAID and MNPVISLABEL) Cf. section 3.2, 3.3 for further details	IREC, EREC, CTMR	F, PP	DA, T	Logrank test, median with confidence interval, HR with confidence interval by Cox model; Kaplan-Meier estimation of rate at 6 months with CI
EFFICACY, DURATION OF RESPONSE				
• Similar to PFS, but based only on the patients having achieved at least PR as best response Cf. section 3.2, 3.3 for further details		(F)	DA	

df = derived from; F = full analysis set; PP = per protocol set; S = safety analysis set; SQL = Standard Query Language; DA = descriptive analysis; HIS = histogram; T = Significance test; * according to eCRF description ([e]mnpimp…) and appendix 1.

PARAMETER / ANALYSIS DESCRIPTION	**CRF PAGE***	**ANALYSIS SET**	**METHODS**	**COMM.**
EFFICACY, OVERALL SURVIVAL, INCL. FOLLOW-UP DURATION				
• Follow-up duration Based on overall survival time periods determined for each patient (see below), independent of censoring		F	DA	
• Overall survival, Kaplan-Meier providing number of events and censored patients Events based on end-of-study information (STUD_ENDE_ART and STUD_ENDE_DAT; to be cross-checked with UEB_STATUS from table OSST). Otherwise [if not selected in the procedure above] censored at maximum observation date according to these eCRF forms; calculated from day of randomization cf. sections **3**.2**,** 3.3 for further details	EOS, OSST, KU_V	F	DA, T	Logrank test, median with confidence interval, HR with confidence interval by Cox model

df = derived from; F = full analysis set; PP = per protocol set; S = safety analysis set; SQL = Standard Query Language; DA = descriptive analysis; HIS = histogram; T = Significance test; * according to eCRF description ([e]mnpimp…) and appendix 1.

PARAMETER / ANALYSIS DESCRIPTION	CRF PAGE*	ANALYSIS SET	METHODS	COMM.
END OF STUDY				
• Type of end of study	EOS	F	DA	STUD_ENDE_ ART
• Causes of death, pre-defined categories	EOS	F	DA	TODESUR SACHE
• Details for death due to toxicity		F	List	TOD_TOX_TEXT

df = derived from; F = full analysis set; PP = per protocol set; S = safety analysis set; SQL = Standard Query Language; DA = descriptive analysis; HIS = histogram; T = Significance test; * according to eCRF description ([e]mnpimp…) and appendix 1.

PARAMETER / ANALYSIS DESCRIPTION	CRF PAGE	ANALYSIS SET	METHODS	COMM.
TOXICITY / SAFETY DURING TREATMENT PERIOD				
• Total number of AEs and SAEs, respectively	AE	S	DA	SAE: SAE_REPORT=2
• Adverse events: maximum CTCAE severity grade (1-5) (AE_GRAD) by patient and by CTCAE category for all AE categories observed	AE	S	SQL, DA	
• Adverse effects: maximum CTCAE severity grade (1-5) (AE_GRAD) by patient and by CTCAE category for all AE categories observed, but limited to events that are causally “related” to either pembrolizumab or radiotherapy	AE	S	SQL, DA	
• Rate of patients with SAE	AE	S	DA	based on SAE_REPORT

df = derived from; F = full analysis set; PP = per protocol set; S = safety analysis set; SQL = Standard Query Language; DA = descriptive analysis; HIS = histogram; T = Significance test; * according to eCRF description ([e]mnpimp…) and appendix 1.

PARAMETER / ANALYSIS DESCRIPTION	CRF PAGE	ANALYSIS SET	METHODS	COMM.
QUALITY OF LIFE				
• Descriptive analysis of all EORTC QLQ C30 subscales at all protocol-defined time points, according to analysis instructions of the EORTC Scoring Manual, issued by the EORTC Data Centre	QLQ	F	DA	
• Descriptive analysis of all EQ-5D-5L questions (proportions of categorical responses) at all protocol-defined time points, from screening to 24 months, with at least 20 valid observations (both arms combined), according to analysis instructions of the EuroQol Research Foundation	EQ	F	DA	
• Descriptive analysis of all EQ-5D-5L VAS question (as continuous variable) at all protocol-defined time points, from screening to 24 months, with at least 20 valid observations (both arms combined), according to analysis instructions of the EuroQol Research Foundation	EQ	F	DA	GESUNDHEIT_ SKALAWERT

df = derived from; F = full analysis set; PP = per protocol set; S = safety analysis set; SQL = Standard Query Language; DA = descriptive analysis; HIS = histogram; T = Significance test; * according to eCRF description ([e]mnpimp…) and appendix 1.

Biomarker / translational research, including the prognostic/predictive impact of PD-L1 on the primary clinical efficacy endpoint, is not included in this plan (analysis by external institution).

Other subgroup/prognostic analyses, considering baseline clinical and biomarker parameters, may be performed exploratively according to the methods described in section 3. Data listings on biomarker/translational categories of the individual patients will be provided by the respective institutions analysing these parameters. A decision on such additional, optional analyses to be performed will be based on the results in the report described above. On publication or presentation, they have to be clearly described as "post-hoc".

4. INTERIM AND FINAL ANALYSES

According to protocol section 8.4, no interim analyses for efficacy are performed. The final analysis will be performed at the end of the follow-up period, after collection and monitoring of all the relevant patient documentation, the PAM, and closure of the database.

5. PRE-ANALYSIS MEETING(S)

Before performing any analyses of clinical data collected within this study, a pre-analysis meeting was held on February 12th, 2025 (cf. ICH E9 Guideline, section 7.1), focusing on the following topics:

- Assessment of patients with major protocol violations (e.g.: with severe violation of in/exclusion criteria before randomisation, with unauthorized treatment before reaching a primary or secondary endpoint event etc.), with respect to their allocation to analysis sets and/or their exclusion from analyses and/or their time-to-event endpoint event categorisation (event counted, event ignored, or censoring). Lists of such patients/violations to be discussed are provided by Monitoring / Data Management, according to SOPs.
- Definition of a “Per-protocol” population.
- Details on coding of AEs.
- Amendments to this SAP, which may be required by protocol amendments, the actual course of study enrolment and treatment, or important new information from outside the trial.
- Additional definitions or decisions, if required for specific items of the analysis.

Participants of the meeting included at least the LKP and persons responsible for the trial coordination / data management, and the statistical analysis. Whenever possible, the review and decisions will be performed blinded with respect to the main efficacy variables.

6. SOFTWARE

All analyses will be performed with established procedures based on the SQL and R/S language.

Düsseldorf, 12.02.25

CCRC
Dr. Axel Hinke

Approved:

Coordinating Investigator

14.02.2025
Date

Prof. Dr. med. Rainer Fietkau

Project Manager at the sponsor (Univ. Erlangen)

14.02.2025
Date

Appendix 1

Description of eCRF forms and corresponding data table short name

eCRF form / data table name according to data description by data management ([e]mnpimp…)	**Short code of table(s)***
Ae	*AE*
Eq_5d_5l	*EQ*
Er_ct_mrt	*CTMR*
Fm	*FM*
Inf_consent	*INF*
Irecist = initial restaging	*IREC*
Ku_screening	*KUSC*
Ku_verlauf	*KU_V*
Pembro	*PEM*
Pembro_gesamt (including EOT)	*EOT*
Pt	*PT*
Qlq_c30	*QLQ*
Radiotherapie	*RAD*
Randomisation	*RAN*
Raucher_krank_ther	*RKT*
Recist = further restaging	*EREC*
Rezidiv	*REZ*
Stud_ende	*EOS*
Ueb_leb_status	*OSST*

* as applied in section 3.4