Summary of the Trial Report
[Synopsis according to ICH E3]

Postoperative adjuvant radiochemotherapy (aRCH) with Cisplatin (C) versus aRCH with C and Pembrolizumab (P) in locally advanced head and neck squamous cell carcinoma (HNSCC); multicenter randomized Phase II study within the German interdisciplinary study group of German Cancer Society (IAG KHT); Pembro-Adjuvant-highRisk

A prospective, open, randomized, controlled multicentre trial

ADRISK

Name of Finished Product/Name of Active Substance:
Pembrolizumab
Indication/Diagnosis:
Advanced primary resectable stage III, IVA/B head and neck squamous cell carcinoma (HNSCC)
Phase of Development:
II
EudraCT-Number:
2017-002546-74
Registration-Number:
ClinicalTrials.gov - No.: NCT03480672

Date of report: 19.01.2026
Version: final 1.0

Trial start: 06.08.2018
End of Trial: 30.01.2025

Coordinating Investigator

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Sponsor

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Signatures

The signing authors approve the report presented here by their signature. The described clinical trial was conducted according to the Declaration of Helsinki, Good Clinical Practice (GCP) as well as the applicable statutory provisions.

Legal representative of the sponsor and coordinating investigator
Prof. Dr. Andreas Dietz

Date

19.01.2026

Biometry
Dr. Annegret Franke

19.01.2026

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1 Name of the Sponsor

Name of institution: Leipzig University

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2 Name of Finished Product	3 Name of active Ingredient
Keytruda®	Pembrolizumab

4 Individual study table

Not applicable

5 Title of Study

Postoperative adjuvant radiochemotherapy (aRCH) with Cisplatin (C) versus aRCH with C and Pembrolizumab (P) in locally advanced head and neck squamous cell carcinoma (HNSCC); multicenter randomized Phase II study within the German interdisciplinary study group of German Cancer Society (IAG KHT); Pembro-Adjuvant-highRisk: trial protocol final 8.0; 10.07.2023

including

- amendment 01; final 3.0; 06.02.2019
- amendment 02; final 4.0; 12.07.2019
- amendment 03; final 5.0; 14.10.2020
- amendment 04; final 6.0; 27.05.2021
- amendment 05; final 7.0; 09.06.2022
- amendment 06; final 8.0; 10.07.2023

➢ **with amendment01:**

Changes in *patient informed consent* (e.g., new side effects and changes in the frequency of side effects) and minor changes at *trial protocol* → according to the sponsor's assessment without relevance for safety or efficacy

- **with amendment02:**

Changes in *patient informed consent* (e.g., new side effects and changes in the frequency of side effects) and minor changes at *trial protocol* → according to the sponsor's assessment without relevance for safety or efficacy

- **with amendment03:**

Changes in *patient informed consent* (e.g., new side effects and changes in the frequency of side effects; change to data protection section due to new requirements) and minor changes in the *trial protocol* (e.g., prolongation of the recruitment time; more detailed explanation of time lines in visit schedule) → according to the sponsor's assessment without relevance for safety or efficacy

- **with amendment04:**

Changes in *patient informed consent* (e.g., new side effects and changes in the frequency of side effects) and minor changes at *trial protocol* (e.g., clearer definition of the starting of reporting period/obligation of AE/SAE; primary endpoint events were specified on the basis of the experience gained during the course of the trial) → according to the sponsor's assessment without relevance for safety or efficacy

- **with amendment05:**

Changes in trial protocol: Prolongation of recruitment time

- **with amendment06:**

Changes in *patient informed consent* (e.g., new side effects and changes in the frequency of side effects) and changes at *trial protocol* (e.g., a shortened follow-up period for the last patients due to premature end of the trial) → according to the sponsor's assessment without relevance for safety or efficacy

6 Investigator	7 Study Centre(s)
see appendix 21.1	see appendix 21.1

8 Publications

Postoperative adjuvant radiochemotherapy with cisplatin versus adjuvant radiochemotherapy with cisplatin and pembrolizumab in locally advanced head and neck squamous cell carcinoma - the study protocol of the ADRISK trial.
Wiegand S, Wichmann G, Vogt J, Vogel K, Franke A, Kuhnt T, Lordick F, Scheuble AM, Hambsch P, Brossart P, Bauernfeind FG, Kaftan H, Maschmeyer G, Paland M, Münter M, Lewitzki V, Rotter N, Stromberger C, Beck M, Dommerich S, Gauler TC, Hapke G, Guntinas-Lichius O, Schröder U, Görner M, Hautmann MG, Steger F, Tamaskovics B, Schmiedeknecht A, Dietz A., Front Oncol. 2023 Mar 21; 13:1128176

Postoperative adjuvant radiochemotherapy with cisplatin (aRCH) vs. aRCH plus pembrolizumab in locally advanced head and neck squamous cell carcinoma (HNSCC): First data of the ADRISK trial

A. Dietz, S. Wiegand, J. Vogt, K. Vogel, A. Schmiedeknecht, A. Schrock, T. Kuhnt, P. Hambsch, N. Nicolay, F. Lordick, A.M. Scheuble, P. Brossart, F.-G. Bauernfeind, G. Feldmann, S. Parade, H. Kaftan, S. Wohlfarth, M. Jungehülsing, M. Paland, G. Maschmeyer, G. Hapke, P. Ebeling, N. Rotter, A. Affolter, M. Muenter, F. Zangos, D. Hahn, V. Lewitzki, U. Müller-Richter, S. Hackenberg, C. Stromberger, M. Heiland, S. Dommerich, M. Beck, T.C. Gauler, S. Lang, B.F. Tamaskovics, W. Budach,U. Schroeder, D. Rades, M. Görner, M. Hautmann, F. Steger, O. Guntinas-Lichius, K. Pietschmann, M. Pirlich, T. Wald, A. Franke, G. Wichmann,
Proffered Paper presentation at European Society for Medical Oncology 2025, Berlin, 18 October 2025

9 Studied period (in years)

Date of first enrolment: 06.08.2018

Date of last completed: 30.01.2025

10 Phase of Development

Phase II

11 Objectives

Primary objective:
To show that addition of Pembrolizumab (P) to postoperative adjuvant radiochemotherapy (aRCH) with Cisplatin (C) improves **event free survival (EFS)** compared with aRCH alone in locally advanced intermediate and high-risk head and neck squamous cell carcinoma (HNSCC).
Hypothesis:
Additional Pembrolizumab increases EFS after 2 years in subjects with locally advanced resectable intermediate and high-risk HNSCC treated with primary surgery and aRCH by 15 % point from 55 % to 70 %.

Secondary objectives:
To show that addition of Pembrolizumab (P) to postoperative adjuvant radiochemotherapy (aRCH) with Cisplatin (C) improves **overall survival (OS)** compared with aRCH alone in locally advanced intermediate and high-risk head and neck squamous cell carcinoma (HNSCC).
To assess toxicity and show that addition of Pembrolizumab (P) to postoperative adjuvant radiochemotherapy (aRCH) with Cisplatin (C) is safe in terms of toxicity.
Hypotheses:
Additional Pembrolizumab increases 2 years OS in subjects with locally advanced resectable intermediate and high-risk HNSCC treated with primary surgery and aRCH.
Additional Pembrolizumab shows an acceptable level of toxicity as compared to aRCH alone.

12 Methodology

ADRISK was a prospective, randomized, and controlled, open-label 2-armed trial.
Patients were randomized 1:1 either to the experimental arm, pembrolizumab (maximally 18 infusions in 3 weekly cycles) **in combination with** adjuvant radio-chemotherapy, or to the standard arm with adjuvant radio-chemotherapy alone. Randomisation of patients was performed centrally in the eCRF provided by the ZKS Leipzig. The randomisation procedure was based on a minimisation algorithm as described in ZKS standard operating procedures for biometrical procedures.
Descriptive analyses concerning enrolment, trial conduct, protocol adherence and safety issues were regularly reviewed by a Data Monitoring and Safety Committee (DMSC). Overall,

six DMC-meetings took place. As a result of all meetings, the members recommended continuing the trial without changes.

13 Number of patients (planned and analysed)

Planned number:
to be allocated to trial: 240 (120 patients per treatment arm)
to be analysed: 240 patients

With amendment 06 reduction of the total trial duration and premature end of the trial had to be brought into effect due to financial and organisational reasons.
This resulted in a reduced number of randomized patients compared to the planned number of patients and a reduced follow-up period of the latest enrolled patients.

Registered patients:	220
Randomized patients:	211 (of 240 planned at the start of trial)
Analyzed patients:	204
Drop-outs before therapy:	7 after randomization (excluded from the Full Analysis Population according to Clinical Trial Protocol)

For details see the CONSORT flow diagram in appendix 21.3.

14 Diagnosis and main criteria for inclusion

Diagnosis	Advanced primary resectable stage III, IVA/B head and neck squamous cell carcinoma (HNSCC) Note! Staging must be done according to the TNM classification version 7th edition
Key inclusion criteria	1. Macroscopically complete resection of newly diagnosed advanced squamous-cell carcinoma arising in the oral cavity, oropharynx, larynx, or hypopharynx 2. Advanced stage III, IVA/B HNSCC according to the TNM classification version 7th edition 3. Eastern Cooperative Oncology Group performance status of 0 to 1 4. Had either intermediate or high-risk characteristics, i.e. any or all of the following: • histologic evidence of invasion of two or more regional lymph nodes • extracapsular extension of nodal disease, • microscopically involved mucosal margins of resection (R1) or margins of resection ≤ 5mm (R0)

	5. Had pathological histologic assessment of p16 (only oropharyngeal carcinoma) 6. Be ≥ 18 years 7. Written informed consent 8. Demonstrate adequate organ function 9. Female subject of childbearing potential should have a negative pregnancy test within 3 days prior to receiving the first dose of study medication. 10. Female subjects of childbearing potential must be willing to use an adequate method of contraception as outlined in Section trial protocol, for the course of the study through 120 days after the last dose of study medication. 11. Reproductive male subjects must agree to use an adequate method of contraception as outlined in Section trial protocol, starting with the first dose of study therapy through 120 days after the last dose of study therapy
Key exclusion criteria	1. Currently participation in any other interventional clinical trial or participation in any other interventional trial within one month before enrolment into this trial. 2. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days before enrolment into this trial. 3. Has a known history of active TB 4. Hypersensitivity to Pembrolizumab or comparable medicinal products or any of its excipients. 5. Has had a prior anti-cancer monoclonal antibody therapy within one month before enrolment into this trial or who has not recovered from adverse events due to agents administered more than one month earlier. 6. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within one month before enrolment into this trial or who has not recovered from adverse events due to a previously administered agent. 7. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer. 8. Has active autoimmune disease that has required systemic treatment in the past 2 years prior to enrolment. Replacement therapy is not considered a form of systemic treatment.

	9. Has evidence of interstitial lung disease or history of (non-infectious) pneumonitis that required steroids within the last 6 months before enrolment into this trial, or current pneumonitis. 10. Has an active infection requiring systemic therapy. 11. Suspected lack of compliance 12. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the baseline visit through 120 days after the last dose of trial treatment. 13. HIV, HBV or HCV infection 14. Has received a live vaccine within one month of enrolment. 15. Hypersensitivity to Cisplatin or any of its excipients 16. Has any potential relationship to the investigator/his deputy or to medical staff of the study team, to the coordinating investigator or is an employee of the study site

15 Information on the Test Product

Dose:

- Pembrolizumab, 200 mg per infusion, in 3-week cycle, applied in maximally 18 cyles within the 1st year of trial

in combination with:

- standard treatment (adjuvant radio-chemotherapy):
  Radiotherapy: standard adjuvant radiotherapy (e.g., pN0 50 Gy; pN1 56 Gy; pECS + primary 66 Gy)
  Chemotherapy: (according to the respective standard of the trial site)
- Cisplatin cumulative dose 300 mg/m^2 body surface according to Cooper/Bernier (Cooper et al. 2004; Bernier et al. 2004),
  or
- Cisplatin cumulative dose: 280 mg/m^2 body surface, e.g., Cisplatin 40 mg/m^2 iv, weekly in 1-7th week of treatment

  In the case of a cisplatin intolerance (e.g., resulting in relevantly impaired function of kidneys) during aRCH, it was possible to switch to carboplatin → implementation in trial protocol was done with amendment 01.

Mode of Administration: intravenous infusion

Batch numbers pembrolizumab:

R001535
S030126
S030126
S030126
T008137
T042518
U014811
W003314
W031462
X018624

16 Duration of Treatment

- 12 months, in 3-week cycles

Patients were treated as usual with aRCH over seven weeks **and in addition** with **18 three-weekly cycles** of Pembrolizumab, resulting in an overall treatment period of 12 months, followed by an observational period over further 12 months (follow up).

17 Reference Therapy

Dose:

- adjuvant radio-chemotherapy:
  Radiotherapy: standard adjuvant radiotherapy (e.g., pN0 50 Gy; pN1 56 Gy; pECS + primary 66 Gy)
  Chemotherapy: (according to the respective standard of the trial site)
- Cisplatin cumulative dose 300 mg/m^2 body surface according to Cooper/Bernier (Cooper et al. 2004; Bernier et al. 2004),
  or
- Cisplatin cumulative dose: 280 mg/m^2 body surface, e.g., Cisplatin 40 mg/m^2 iv, weekly in 1-7th week of treatment;
  → A switch to carboplatin (as described in section 15) was allowed.

18 Criteria for Evaluation

18.1 Efficacy

The primary endpoint was Event Free Survival (EFS) defined as time from randomization to the first event, i.e.:

- locoregional or distant recurrence (relapse),
- occurrence of further malignoma (independent from localization and type),
- death from any cause, or
- initiation of a new anti-cancer treatment without a previous EP-event (primarily in case of safety concerns/toxicities observed which must be addressed in patient's treatment).

EFS is an established surrogate parameter for overall survival in locally advanced head and neck cancer (Michiels et al. 2009).

18.2 Secondary Efficacy Outcomes

Overall survival (OS) was defined as time from randomization to death from any cause. OS is the most relevant outcome.

18.3 Safety

Adverse events/Toxicity according to NCI-CTCAE criteria in 35 predefined areas, since a new drug was applied. Further (S)AE could be reported in addition.

19 Statistical Methods/analysis procedures

The trial specific Statistical Analyses Plan (SAP) describes all details of statistical analyses. The confirmatory analysis was performed in the full analysis set (FAS) of patients based on the intention-to-treat principle, see CONSORT flow chart, section 21.3. Randomized patients without any study treatment were excluded from the FAS (according to trial protocol/SAP).
Time to event endpoints were analysed by Cox regression with arm as fixed effects, stratification criteria as fixed and site as random effect. Kaplan-Meier curves provide courses of endpoints per arm.

Assessment of toxicities:
Due to the relevantly longer treatment period in the experimental arm the numbers of (S)AE/ toxicities per arm are not directly comparable.
Comparisons of both arms regarding toxicities comprise the trial phase from visit V1 to visit V5 only, were the aRCH and the Pembro+aRCH regimes are comparable.
Later than V5 when the treatment in experimental arm was continued and toxicity reports were requested only for these patients, so-called “late” toxicities were presented descriptively.

The occurrence of safety endpoints (AE by Preferred Term - PT/occurrences of toxicities of grades ≥3) were compared by chi-squared/ Fisher’s tests.
Serious adverse events / SUSARs were reported descriptively by MedDRA System Organ Class (SOC) and Preferred Term.

No confirmatory subgroup analyses were planned. However, various subgroups were analyzed for descriptive reasons, in the majority already predefined in the SAP to allow a comprehensive overview on study results for publication.

Safety analyses comprised all predefined toxicities, most frequently reported further AE as well as combined toxicities of following organ systems (as detailed in the statistical analyses plan):

1. Liver
2. Kidney
3. Thyroid gland
4. Skin and subcutanous tissues
5. Blood and vascular disorders
6. Respiratory, thoracic and mediastinal disorders
7. Ear and labyrinth disorders
8. Gastrointestinal disorders
9. Metabolism and nutrition disorders
10. General symptoms & signs / Infections
11. Nervous system disorders.

20 Summary/Conclusion

20.1 Efficacy results

Primary Endpoint: Event-free Survival (EFS)

The Kaplan-Meier curves show no relevant differences between the arms.
The EFS rates per arm after 36 months and 24 months are shown in the following figure: the unadjusted HR [95 % confidence limits] for EFS is HR 0.88, 95% confidence interval [0.53; 1.44], see Figure 1.

Corresponding to this results no significant arm differences regarding the efficacy of pembrolizumab in terms of EFS were found in the confirmatory analysis (p=0.423, Table 2). No hints on a violation of the proportional hazards' assumption were found (p=0.996 for rando arm; p= 0. for the model p=0.798).

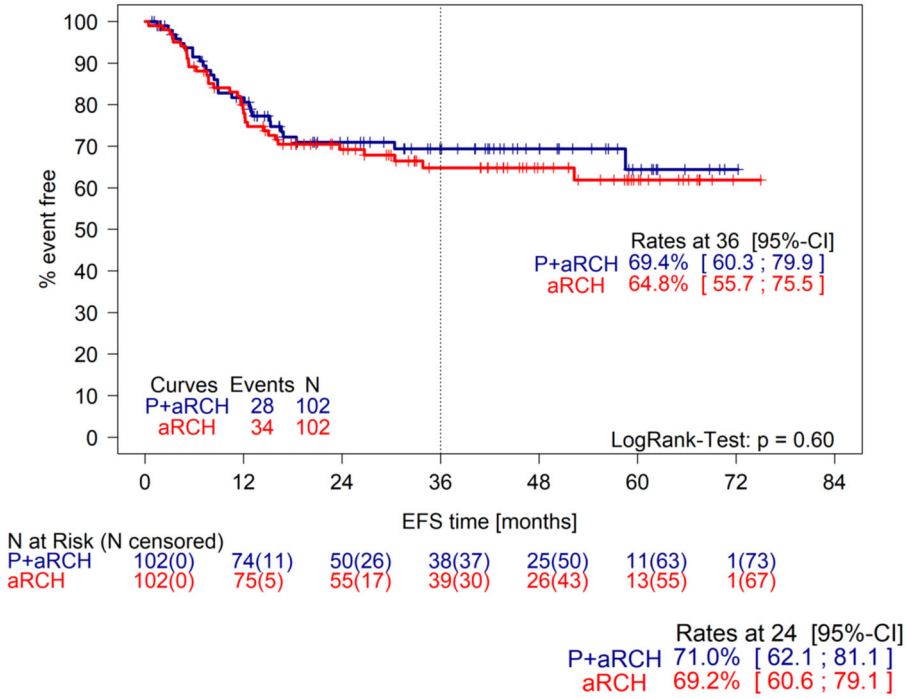


Figure 1: Kaplan-Meier curves for EFS, including rates at 24 months and 36 months

Covariates	Coef	seCoef	lowerCoef95	upperCoef95	HR=exp(coef)	lowerHR95	upperHR95	p.value
RandoarmP+aRCH	-0.133	0.255	-0.633	0.368	0.876	0.531	1.444	0.603

Table 1: Results of univariate Cox regression model for EFS

Covariates	Coef	seCoef	lowerCoef95	upperCoef95	HR=exp(coef)	lowerHR95	upperHR95	p.value
Cov_LOK4Oral cavity	0.953	0.410	0.149	1.757	2.592	1.160	5.792	0.020
Cov_LOK4Oropharynx-p16-	0.736	0.432	-0.110	1.582	2.088	0.896	4.865	0.088
Cov_LOK4Oropharynx-p16+	-1.025	0.466	-1.938	-0.111	0.359	0.144	0.895	0.028
Cov_CisRegimeQ3w	0.310	0.280	-0.237	0.858	1.364	0.789	2.359	0.267
RandoarmP+aRCH	-0.209	0.261	-0.720	0.302	0.812	0.487	1.353	0.423

Table 2: Results of strata-adjusted Cox regression model for EFS; confirmatory analysis

Secondary Endpoint: Overall Survival (OS)

In OS as major secondary endpoint, no significant arm differences (p=0.554, see Table 4) regarding the efficacy of pembrolizumab were found as well. The test for proportional hazards also gave no hints on a violation on proportional hazard assumption wither p values 0.207 (for rando arm) and p=0.568 (for model).

The Kaplan-Meier curves for OS and OS rates per arm after 36 months and 24 months shown in Figure 2 also show no relevant differences between the arms.
The unadjusted HR [95 % confidence limits] for OS is 0.85 [95 %-CI: 0.46; 1.55].

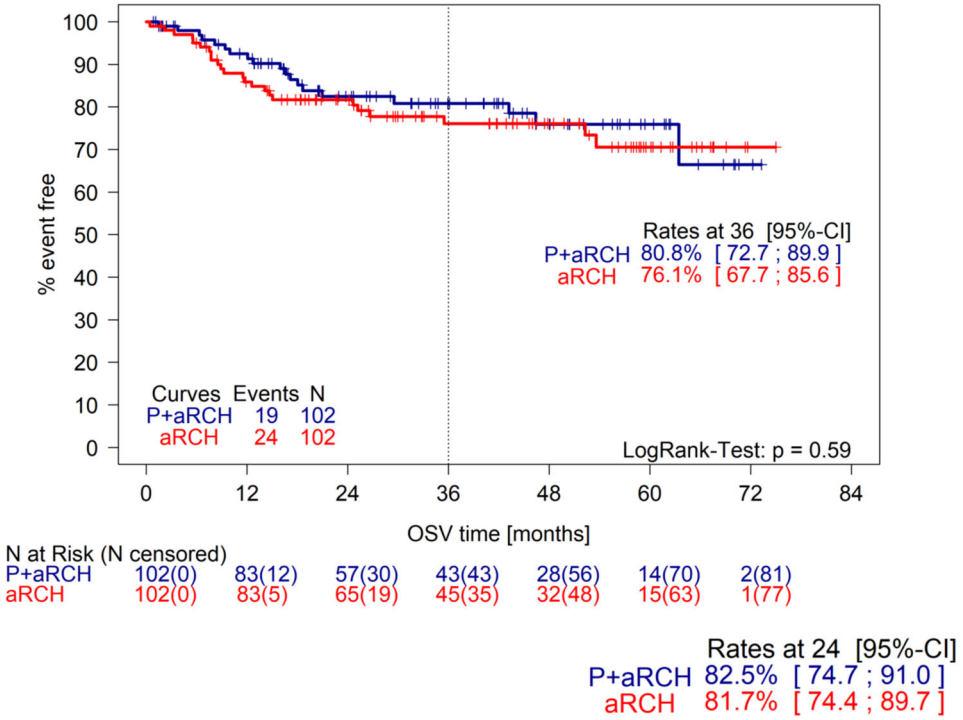


Figure 2: Kaplan-Meier curves for OS, including rates at 24 months and 36 months, in the FAS

Covariates	Coef	seCoef	lowerCoef95	upperCoef95	HR=exp(coef)	lowerHR95	upperHR95	p.value
RandoarmP+aRCH	-0.165	0.307	-0.767	0.437	0.848	0.464	1.548	0.591

Table 3: Results of univariate Cox regression model for OS

Covariates	Coef	seCoef	lowerCoef95	upperCoef95	HR=exp(coef)	lowerHR95	upperHR95	p.value
Cov_LOK4Oral cavity	0.411	0.436	-0.445	1.266	1.508	0.641	3.546	0.347
Cov_LOK4Oropharynx-p16-	0.147	0.475	-0.783	1.078	1.159	0.457	2.938	0.756
Cov_LOK4Oropharynx-p16+	-1.295	0.502	-2.280	-0.311	0.274	0.102	0.733	0.010
Cov_CisRegimeQ3w	0.355	0.326	-0.283	0.993	1.426	0.753	2.700	0.276
RandoarmP+aRCH	-0.183	0.310	-0.792	0.425	0.832	0.453	1.529	0.554

Table 4: Results of strata-adjusted Cox regression model for OS

Analyses within the per-protocol set of patients as defined in the SAP gave no deviating results compared to the FAS results with p_{EFS}=0.391 p_{OS}=0.247.

In spite of a wide variety of descriptive EFS (and OS) subgroup analyses very few characteristics showed a differential efficacy of pembrolizumab (Figure 3 as most comprehensive example for EFS). Only in 4 out of more than 30 sub-group analyses (acc. to SAP), raw p values of <0.1 (without adjustment for multiple testing) were observed, either in one subgroup or in the subgroup x arm interaction as shown for:

- (female) sex,
- (never) smoking history, and
- TNM-classification (<T4 or >N2a).

However, those subgroups showed either few events and/or few patients. Thus, the imbalance may possibly result from patient-specific characteristics than from beneficial treatment effects in either subgroup.

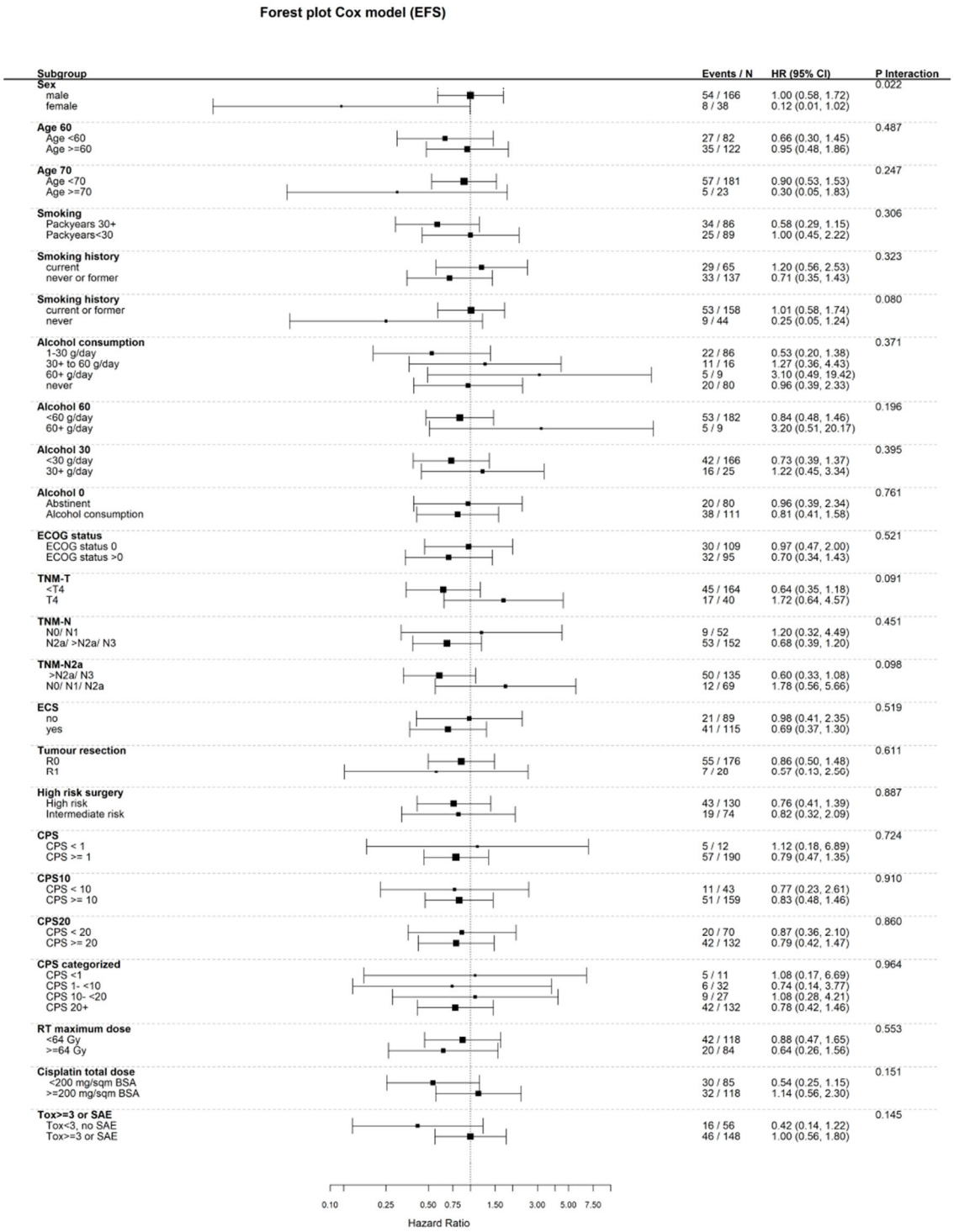


Figure 3: Forest plot for EFS in a selection of subgroup analyses

20.2 Safety results

In the ADRISK trial the Safety Analysis Population is identical to the Full Analysis Population. In total, 66.76 patient-years under intervention were observed in the Pembro+aRCH arm and 10.09 patient-years in the aRCH arm, due to the relevantly longer treatment period in the experimental arm. Therefore, the numbers of (S)AE per arm are not directly comparable due to the relevantly different durations of treatment.

In total, 372 SAE in 124 patients were reported, thereof

- 242 SAE in 70 patients of the experimental arm, and

- 130 SAE in 54 patients of the standard arm.

A separate appendix covers the SAE summary tabulation of the ADRISK trial:
<ADRISK_Summary-tabulation_all-SAEs_2025-07-23.pdf>

Separate appendices refer to SAEs possibly related to one of the IMPs, either by investigator's or by sponsor's assessment (SAR):
<ADRISK_Summary-tabulation_all-SARs_Pembrolizumab_2025-07-23.pdf>
<ADRISK_Summary-tabulation_all-SARs_Cisplatin_2025-07-23.pdf>
<ADRISK_Summary-tabulation_all-SARs_Radiotherapy_2025-07-23.pdf>
<ADRISK_Line-Listing_all-SARs_2025-07-23.pdf>.

In total, 43 deaths were reported, thereof 19 in the experimental arm and 24 in the standard arm.

According to the SAP, arm comparisons were defined for acute toxicities/further AE up to V5 while late toxicities within the experimental arm were described separately up to the end of data collection.

Details on acute toxicities up to visit 5

In five of 204 randomised and treated patients exclusively toxicities with CTCAE grades = 0 were reported, for one patient no toxicity reports were available despite repeated requests.

Max. CTC-grad per patient	Pembrolizumab + aRCH	Pembrolizumab + aRCH [%]	aRCH	aRCH [%]	All	All [%]
0	3	3.0	2	2.0	5	2.5
1	1	1.0	7	6.9	8	3.9
2	29	28.7	28	27.5	57	28.1
3	57	56.4	60	58.8	117	57.6
4	11	10.9	5	4.9	16	7.9
Nvalid	101	100.0	102	100.0	203	100.0

Table 5: maximum CTCAE grade in predefined toxicities during intervention per patient by arm

In 65 aRCH patients (standard) and 69 Pembro+aRCH patients (experimental), toxicities with CTCAE grade ≥ 3 were reported at least once up to visit V5; see following table by term:

Toxicity (CTC-grade >=3)	Pembrolizumab + aRCH	Pembrolizumab + aRCH [%]	aRCH	aRCH [%]	All	All [%]
Allergic reaction	1	0.4	0	0.0	1	0.2
Anaemia	14	5.7	4	2.0	18	4.0
Aspiration	0	0.0	1	0.5	1	0.2
Decreased appetite	9	3.6	9	4.5	18	4.0
Diarrhoea	3	1.2	0	0.0	3	0.7
Drug-induced hypersensitivity syndrome	1	0.4	0	0.0	1	0.2
Dry mouth	5	2.0	7	3.5	12	2.7
Dysphagia	47	19.0	35	17.5	82	18.3
Dyspnoea	1	0.4	0	0.0	1	0.2
Edema	1	0.4	1	0.5	2	0.4
Fatigue	5	2.0	5	2.5	10	2.2
Hepatitis	5	2.0	2	1.0	7	1.6
Hoarseness	2	0.8	2	1.0	4	0.9
Hypomagnesaemia	3	1.2	5	2.5	8	1.8
Hyponatraemia	5	2.0	0	0.0	5	1.1
Leukopenia	32	13.0	29	14.5	61	13.6
Maculo-papular exanthema	1	0.4	0	0.0	1	0.2
Mucositis	49	19.8	44	22.0	93	20.8
Nausea	5	2.0	17	8.5	22	4.9
Neutropenia	13	5.3	6	3.0	19	4.3
Ototoxicity	5	2.0	0	0.0	5	1.1
Pain	16	6.5	13	6.5	29	6.5
Pruritus	2	0.8	0	0.0	2	0.4
Pyrexia	1	0.4	2	1.0	3	0.7
Thrombopenia	6	2.4	2	1.0	8	1.8
Toxicity renal	12	4.9	9	4.5	21	4.7
Vomiting	3	1.2	7	3.5	10	2.2
Nvalid	247	100.0	200	100.0	447	100.0

Table 6: Predefined toxicities with CTCAE grad ≥ 3 by tox term per arm

In the selected predefined toxicities anaemia, maculo-papular exanthema, hyponatraemia, and thyroid gland certain arm differences regarding the maximum CTCAE grades up to visit V5 were observed and presented in the following tables:

Anaemia

Max. CTC-grade for predefined toxicities by rando arm

		Pembrolizumab + aRCH arm		*aRCH arm*		*All*			
Anaemia		N	%	N	%	N	%	p-value	Test used
Max. CTCgrade	0	26	25.7	42	41.2	68	33.5		
	1	32	31.7	34	33.3	66	32.5		
	2	33	32.7	23	22.5	56	27.6		
	3	9	8.9	3	2.9	12	5.9		
	4	1	1.0	0	0.0	1	0.5		
———	**Nvalid**	**101**	**100.0**	**102**	**100.0**	**203**	**100.0**		
At least CTCgrade >0 reported	No	26	25.7	42	41.2	68	33.5		
	Yes	75	74.3	60	58.8	135	66.5		
———	**Nvalid**	**101**	**100.0**	**102**	**100.0**	**203**	**100.0**	**0.029**	**chisq**
CTCgrade >2 reported	No	91	90.1	99	97.1	190	93.6		
	Yes	10	9.9	3	2.9	13	6.4		
———	**Nvalid**	**101**	**100.0**	**102**	**100.0**	**203**	**100.0**	**0.082**	**chisq**

Maculo-papular exanthema

Max. CTC-grade for predefined toxicities by rando arm

		Pembrolizumab + aRCH arm		*aRCH arm*		*All*			
Maculo-papular exanthema		N	%	N	%	N	%	p-value	Test used
Max. CTCgrade	0	93	92.1	101	99	194	95.6		
	1	5	5.0	1	1	6	3.0		
	2	2	2.0	0	0	2	1.0		
	3	1	1.0	0	0	1	0.5		
———	**Nvalid**	**101**	**100.0**	**102**	**100**	**203**	**100.0**		
At least CTCgrade >0 reported	No	93	92.1	101	99	194	95.6		
	Yes	8	7.9	1	1	9	4.4		
———	**Nvalid**	**101**	**100.0**	**102**	**100**	**203**	**100.0**	**0.018**	**fisher**
CTCgrade >2 reported	No	100	99.0	102	100	202	99.5		
	Yes	1	1.0	0	0	1	0.5		
———	**Nvalid**	**101**	**100.0**	**102**	**100**	**203**	**100.0**	**0.50**	**fisher**

Hyponatraemia

Max. CTC-grade for predefined toxicities by rando arm

		Pembrolizumab + aRCH arm		*aRCH arm*		*All*			
Hyponatraemia		N	%	N	%	N	%	p-value	Test used
Max. CTCgrade	0	73	72.3	85	83.3	158	77.8		
	1	17	16.8	17	16.7	34	16.7		
	2	8	7.9	0	0.0	8	3.9		
	3	3	3.0	0	0.0	3	1.5		
———	**Nvalid**	**101**	**100.0**	**102**	**100.0**	**203**	**100.0**		
At least CTCgrade >0 reported	No	73	72.3	85	83.3	158	77.8		
	Yes	28	27.7	17	16.7	45	22.2		
———	**Nvalid**	**101**	**100.0**	**102**	**100.0**	**203**	**100.0**	**0.084**	**chisq**
CTCgrade >2 reported	No	98	97.0	102	100.0	200	98.5		
	Yes	3	3.0	0	0.0	3	1.5		
———	**Nvalid**	**101**	**100.0**	**102**	**100.0**	**203**	**100.0**	**0.12**	**fisher**

Toxicities of thyroid gland

Max. CTC-grade for predefined toxicities by rando arm

		Pembrolizumab + aRCH arm		*aRCH arm*		*All*			
Toxicities of thyroid gland		N	%	N	%	N	%	p-value	Test used
Max. CTCgrade	0	75	74.3	95	93.1	170	83.7		
	1	14	13.9	5	4.9	19	9.4		
	2	12	11.9	2	2.0	14	6.9		
———	**Nvalid**	**101**	**100.0**	**102**	**100.0**	**203**	**100.0**		
At least CTCgrade >0 reported	No	75	74.3	95	93.1	170	83.7		
	Yes	26	25.7	7	6.9	33	16.3		
———	**Nvalid**	**101**	**100.0**	**102**	**100.0**	**203**	**100.0**	**0.0006**	**chisq**
CTCgrade >2 reported	No	101	100.0	102	100.0	203	100.0		
———	**Nvalid**	**101**	**100.0**	**102**	**100.0**	**203**	**100.0**	**-**	**-**

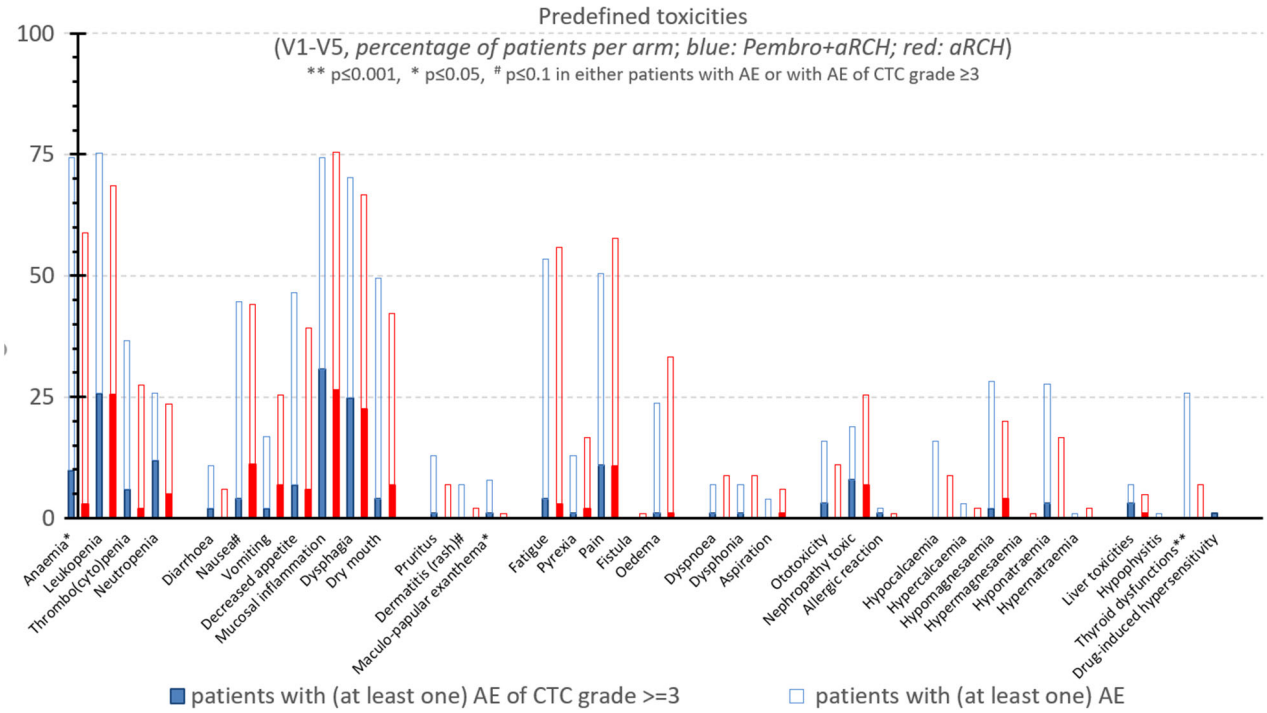


Figure 4: Overview on all predefined toxicities (per patients affected in both arms (** p ≤0.001, *p ≤0.05, # p ≤0.1)

“Late” toxicities regarding pembrolizumab after regular end of aRCH therapy

“Late” toxicities (later than visit 5 = regular end of aRCH treatment, including the period of requested toxicity reporting, as defined within the SAP) were assessed in the experimental arm only during further application of pembrolizumab.
This section present frequencies per predefined toxicity term and aggregated

- in the 3-monthly intervals in-between the previous until the named visit as well as
- until the individual end of pembrolizumab therapy (visit V-PTT[1]= safety visit after End of Pembrolizumab acc. to trial protocol).

Please NOTE:
“Visit 6” (in the header) comprises toxicities after V5 incl. C6, C7, C8, V6=C9 cycles;
“Visit 7” comprises toxicities after V6 incl. C10, C11, C12, V7=C13 cycles;
“Visit 8” comprises toxicities after V7 incl. C14, C15, C16, V17, V8=C18 cycles;
“Visit 6 to V-PTT” comprises toxicities after V5 up to the latest individual toxicity report (V-PTT).

Figure 5 shows all toxicities of CTCAE grade 3 or higher per type and visit in patients of the experimental arm.

[1] ‘**P**embrolizumab **T**reatment **T**ermination’ (PTT) visit, regularly performed 4 weeks after the last pembrolizumab infusion

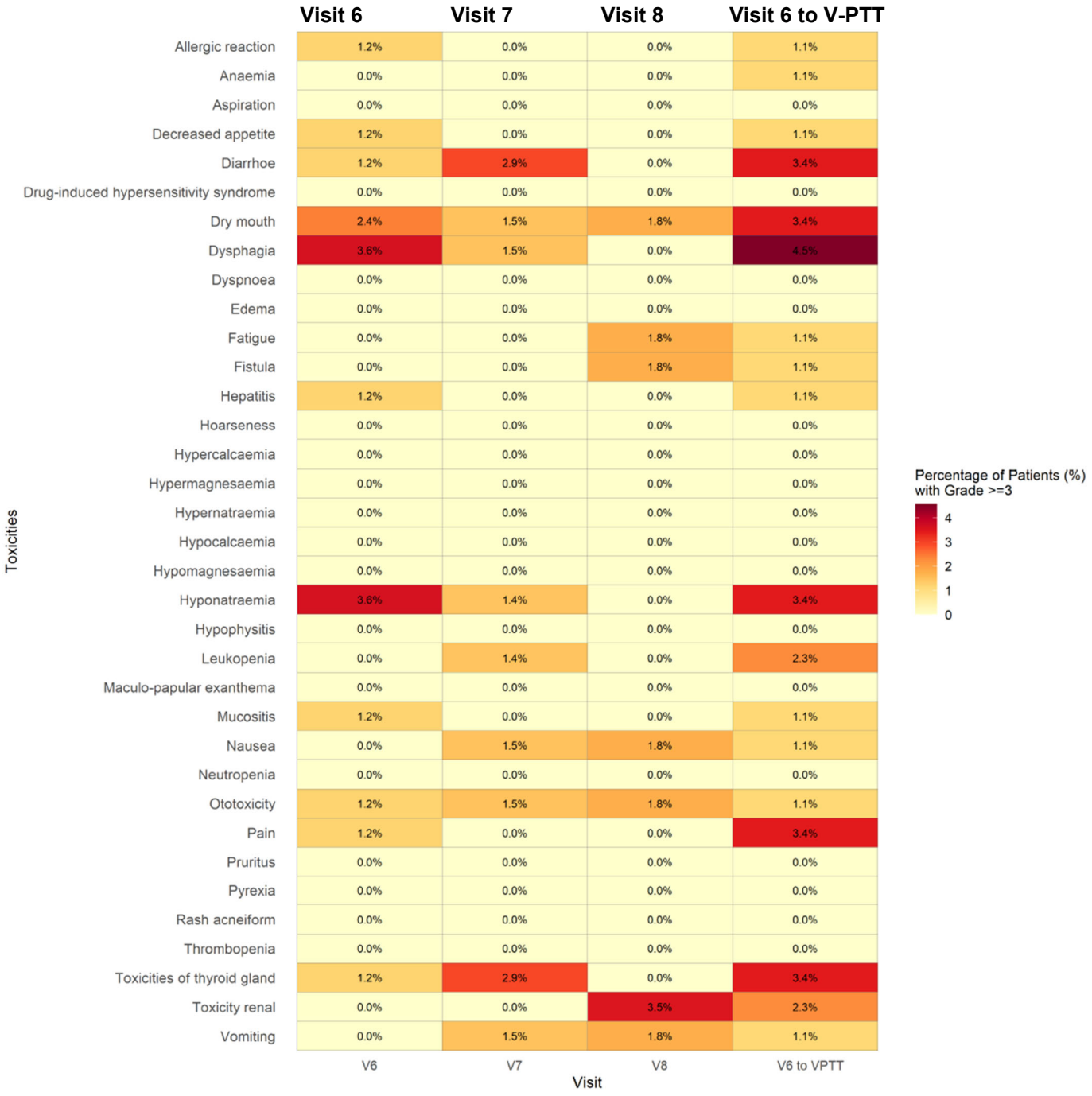


Figure 5: Heat map for late predefined toxicities of CTCAE grade 3 or higher per type and visit in patients of the experimental arm

The percentage of patients who suffered from any predefined toxicity per time interval are shown in Figure 6 below. As Figure 6shown, only a minority of patients reported any late toxicity with CTCAE grades ≥3.

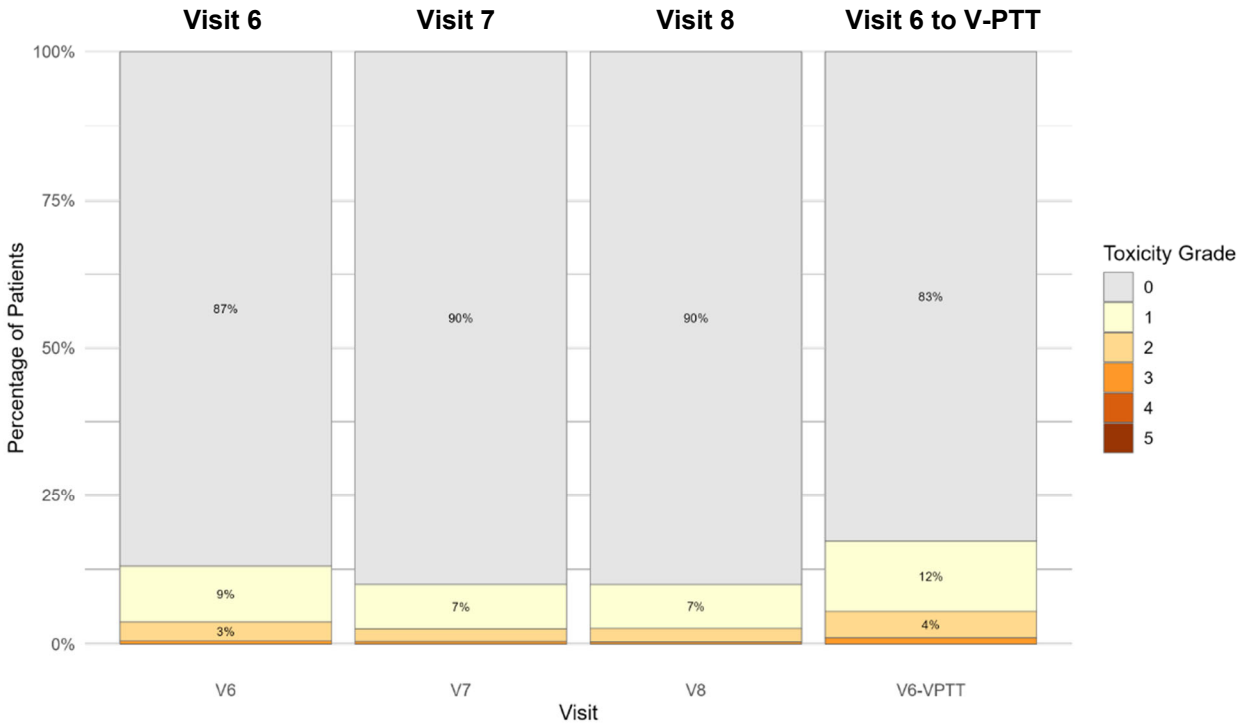


Figure 6: Distribution of late toxicities by CTCAE grade and visit

20.3 Conclusions

Background/Importance:
Primary curative resection of locally advanced HNSCC often reveals pathologically intermediate or high-risk features for relapse requiring adjuvant cisplatin-based radiochemotherapy (aRCH). Adding pembrolizumab to aRCH was investigated to evaluate if it can improve event-free survival (EFS).

Trial design:
The 1:1 randomized phase II trial ADRISK (NCT03480672) aimed to improve EFS (primary endpoint) by adding pembrolizumab to standard aRCH (stratified for p16+/- oropharynx and further localizations, q1w/q3w cisplatin regimen – see section 21.2 for frequencies in strata). 240 patients with 100 events were expected to show significantly improved EFS with 80 % power in a Cox regression model.

Patients and treatment:
From August 2018 until end of November 2023, 211 patients with resected stage III or IV HNSCC of oral cavity, oropharynx, hypopharynx or larynx with pathologic high (R1, extracapsular nodal extension) or intermediate risk (R0 < 5 mm; pN ≥ 2) needing aRCH were randomized, of which 204 were treated. Patients received standard aRCH (64 Gy with 202 mg/m^2 cisplatin [total dose, median]; n = 102, arm A) or aRCH + pembrolizumab (64 Gy, 202 mg/m^2 + 2600 mg; 200 mg iv q3w, max. 12 months; n = 102, arm B).

Outcome:
We present results after >30 months median follow up time. Pembrolizumab improved EFS numerically (28/34 events in pembro+aRCH/aRCH). Due to fewer events than expected, neither EFS (HR 0.81 [95 % confidence interval 0.48; 1.35]; p = .423) nor OS (HR 0.83 [0.45; 1.53]; p = .554) were significantly different to the standard treatment.

Only 11 EFS events (5/6 in pembro+aRCH/aRCH, HR 0.91 [0.28; 2.98]) were observed in p16+ oropharynx patients (HPV-related). This corresponds to 46 % of all patients. All other

patients (= 54 %) had similar benefit (HR 0.89 [0.51; 1.54]) favoring arm pembro+aRCH (51 events, 23/28 in pembro+aRCH/aRCH). The highest difference in EFS events (18/23 in pembro+aRCH/aRCH) was among the 81 HPV-unrelated cases with CPS ≥ 10 (38/43 in pembro+aRCH/aRCH; HR 0.83 [0.45; 1.54]; p = .56).
No new safety signals were detected.

Conclusions and Relevance:
Due to 46 % p16+ oropharynx patients with fewer events, the ADRISK trial could neither demonstrate significantly improved EFS nor OS through added pembrolizumab. Patients with HPV-unrelated, CPS ≥ 10 HNSCC (40 %) might possibly benefit from added pembrolizumab.

Pembrolizumab added to aRCH after resection of high or intermediate risk locally advanced (LA) HNSCC was feasible and safe. No new safety signals were observed in the Pembrolizumab + aRCH arm. Immune-mediated AEs were even less than expected under the combined treatment.

A significantly lower number of events was observed compared to the expected numbers. In the subgroup analyses, no formally significant improvements were seen through additional pembrolizumab application, nor were there any strong signals. Thus, the planned number of patients would not have provided a sufficiently strong (significant) signal regarding the superiority through added pembrolizumab.

In resected intermediate- and high-risk (HPV-related) p16+ oropharynx HNSCC, aRCH as currently established standard treatment is efficient with no unmet clinical need for further escalation.

There is no evidence for substantial improvements by Pembrolizumab + aRCH after surgery without preoperative neoadjuvant treatment.

21 Appendix

21.1 List of Investigators/Study Centres

Investigator	**Trial Site**
Prof. Dr. Andreas Dietz	Universitätsklinikum Leipzig AöR Klinik und Poliklinik für Hals-, Nasen-, Ohrenheilkunde Liebigstrasse 10-14 04103 Leipzig
Dr. Ursula Schröder	Universitätsklinikum Schleswig-Holstein, Campus Lübeck Klinik für Hals-, Nasen- und Ohrenheilkunde Ratzeburger Allee 160 23538 Lübeck
Prof. Dr. Peter Brossart	Universitätsklinikum Bonn Med. Klinik III / ZIM, Hämatologie/Onkologie Sigmund-Freud-Straße 25 53105 Bonn
Prof. Dr. Karin Jordan	Ernst von Bergmann Klinikum Potsdam Zentrum für Hämatologie, Onkologie und Strahlenheilkunde, Klinik für Hämatologie und Onkologie Charlottenstraße 72 14467 Potsdam
Prof. Dr. Holger Kaftan	Helios Klinikum Erfurt GmbH Klinik für Hals-Nasen-Ohrenheilkunde Nordhäuser Straße 74 99089 Erfurt
Dr. Balint Tamaskovics	Universitätsklinikum Düsseldorf Klinik für Strahlentherapie und Radiologische Onkologie Moorenstraße 5, Geb. 13.53 40225 Düsseldorf
Prof. Dr. Marc Münter	Klinikum Stuttgart - Katharinenhospital Klinik für Radioonkologie und Strahlentherapie Kriegsbergstraße 60 MVZ Strahlenambulanz Haus E 70174 Stuttgart
Dr. Felix Steger	Universitätsklinikum Regensburg Klinik und Poliklinik für Strahlentherapie Franz-Josef-Strauß-Allee 11 93053 Regensburg
Dr. Thomas Christoph Gauler	Universitätsklinikum Essen Klinik und Poliklinik für Strahlentherapie Hufelandstraße 55 45147 Essen
Prof. Dr. Orlando Guntinas-Lichius	Universitätsklinikum Jena Klinik für Hals-Nasen-Ohrenheilkunde Am Klinikum 1 07747 Jena
Dr. Victor Lewitzki	Universitätsklinikum Würzburg Klinik und Poliklinik für Strahlentherapie Josef- Schneiderstr. 11

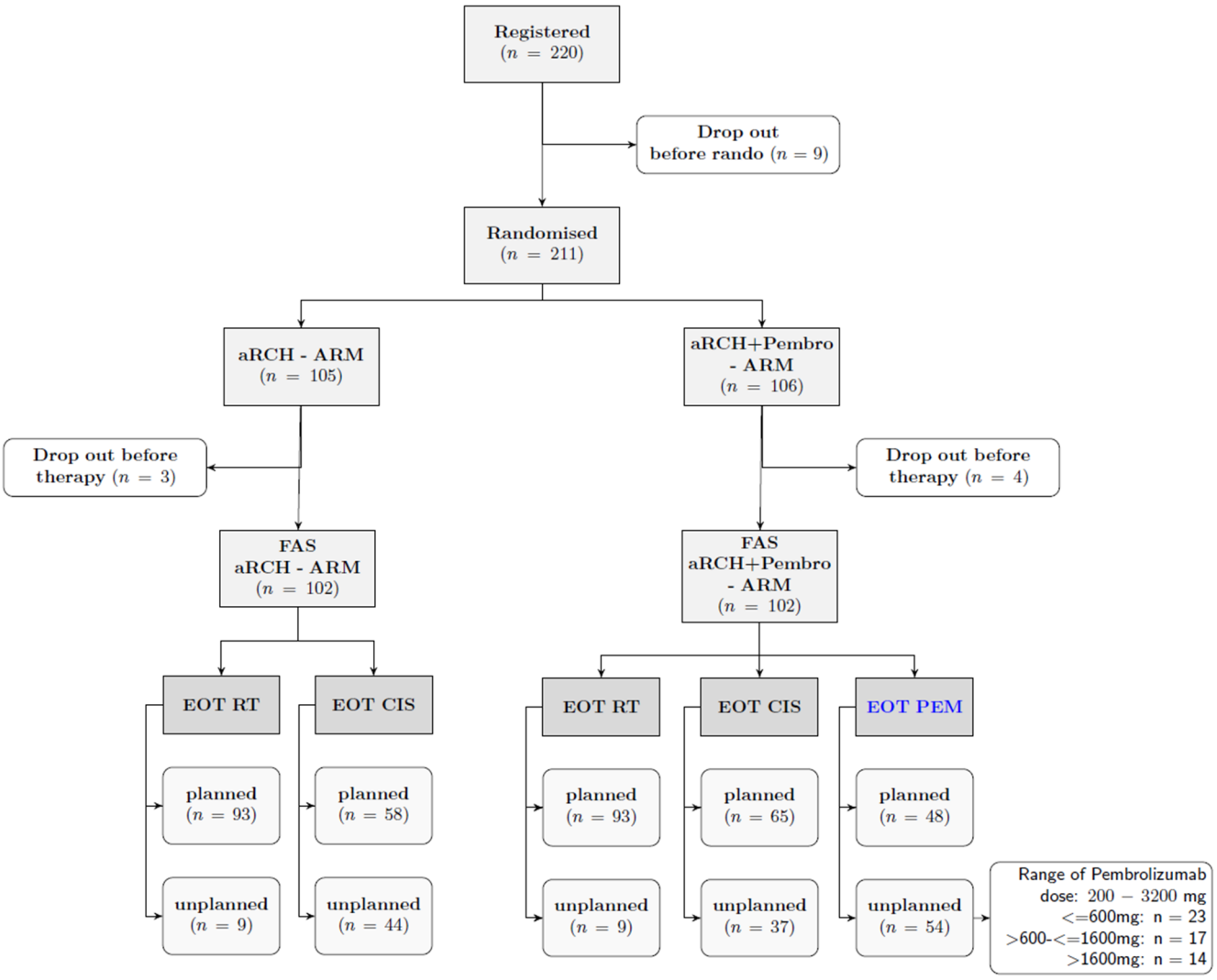
	97080 Würzburg
Prof. Dr. Nicole Rotter	Universitätsklinikum Mannheim Hals-Nasen-Ohren Klinik Theodor-Kutzer-Ufer 1-3 68167 Mannheim
Dr. Steffen Dommerich	Charité - Universitätsmedizin, CVK und CCM Klinik für Hals-Nasen-Ohrenheilkunde Charitéplatz 1 10117 Berlin
PD Dr. Martin Görner	Klinikum Bielefeld Klinik für Hämatologie und Onkologie Teutoburger Straße 50 33604 Bielefeld
Dr. Marcus Beck	Charité Universtiätsmedizin Berlin Klinik f. Radioonkologie u. Strahlentherapie CVK/CBF Augustenburger Platz 1 13353 Berlin
Dr. Gunnar Hapke	Kath. Marienkrankenhaus Hamburg gGmbH Zentrum für Innere Medizin Alfredstraße 9 22087 Hamburg

21.2 Stratification characteristics in randomisation process

Variable	Characteristic	Pembrolizumab + aRCH	Pembrolizumab + aRCH [%]	aRCH	aRCH [%]
Tumor localizations	Oral cavity	24	23.5	19	18.6
	Oropharynx	67	65.7	67	65.7
	Larynx	7	6.9	10	9.8
	Hypopharynx	4	3.9	6	5.9
———	Nvalid	102	100.0	102	100.0
Histopathology [p16-marker]	p16+	46	68.7	47	70.1
	p16-	21	31.3	20	29.9
———	Nvalid	67	100.0	67	100.0
Schedule of chemotherapy	Q3W 3-weekly application	27	26.5	30	29.4
	Q1W weekly application	75	73.5	72	70.6
———	Nvalid	102	100.0	102	100.0

It was found that approximately 66 % of tumors were located in the oropharynx and thereof two third with p16+ histopathololgy, instead of 30% preassumed for this localization and a ratio of 1:2 of p16+.

21.3 CONSORT Flow Diagramm



21.4 Abbreviations

aRCH	adjuvant radiochemotherapy
AE	Adverse Event
AMG	Arzneimittelgesetz
C	Cisplatin
EFS	Event Free Survival
FAS	Full analysis set
GCP	Good Clinical Practice
HNSCC	Head and neck squamous cell carcinoma
HR	Hazard Ratio
LA	locally advanced
LPLV	Last Patient Last Visit
P	Pembrolizumab
PT	Preferred Term
OS	Overall survival
SAE	schwerwiegendes unerwünschtes Ereignis (serious adverse event)
SAP	Statistical Analyses Plan
SAR	schwerwiegende Nebenwirkung (serious adverse reaction)
SOC	System Organ Class
SUSAR	Unerwartete, schwerwiegende Arzneimittelnebenwirkung (suspected unexpected serious adverse reaction)