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

IMPORTANCE

Final Report

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Clinical Trials No.: NCT03386357
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(federführend: Ethikkommission der
Medizinischen Fakultät der Universität Erlangen-Nürnberg)

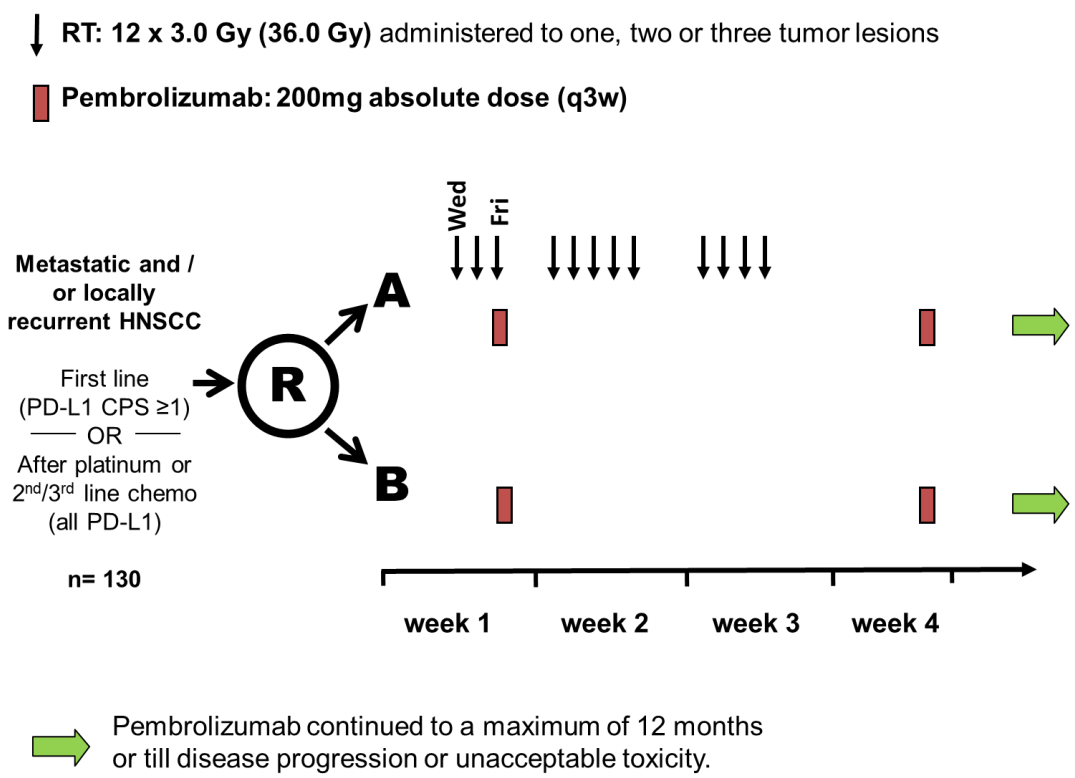
Investigational drugs	Pembrolizumab (MK-3475)
Sponsor	Universitätsklinikum Erlangen, Strahlenklinik, insoweit handelnd für den Freistaat Bayern, vertreten durch den Dekan der Medizinischen Fakultät der Friedrich-Alexander-Universität Erlangen-Nürnberg
Investigator	Prof. Dr. Rainer Fietkau, Strahlenklinik, Universitätsklinikum Erlangen, Universitätsstr. 27, 91054 Erlangen

1	**Name of Sponsor/Company**
	Universitätsklinikum Erlangen, Strahlenklinik, insoweit handelnd für den Freistaat Bayern, vertreten durch den Dekan der Medizinischen Fakultät der Friedrich-Alexander-Universität Erlangen-Nürnberg
2	**Name of Finished Product**
	MK-3475
3	**Name of Active Substance**
	Pembrolizumab / Keytruda
4	**Individual Study Table: Referring to Part of the Dossier (Volume, Page)** **Anmerkung: Diese Angabe ist nur bei Einreichung in Zusammenhang mit einem Zulassungsdossier erforderlich**
	Not applicable
5	**Title of Study** **Anmerkung: Es muss klar hervorgehen, dass die letzte Protokollversion einschließlich aller Amendments gemeint ist, die Amendments sind anzugeben und zu identifizieren**
	Randomized phase II study of immune stimulation with Pembrolizumab and radiotherapy in second line therapy of metastatic head and neck squamous cell carcinoma – Protocol v1.6 Previous Protocol Versions/Amendments: • Protocol v. 1.1 – 03.05.2018 First Submission • Protocol v. 1.2 – 08.11.2018 Amendment 1 • Protocol v. 1.3 – 09.12.2019 Amendment 2 • Protocol v. 1.4 – 18.05.2021 Amendment 3 • Protocol v. 1.5 – 10.04.2022 Amendment 4 • Protocol v. 1.6 – 04.02.2023 Amendment 6 End of Recruitment: 31.05.2025 End of Trial (last patient last visit): 01.10.2024
6	**Investigators**
	Principal Investigator: Prof. Dr. Rainer Fietkau, Universitätsklinikum Erlangen, Strahlenklinik, Universitätsstr. 27, 91054 Erlangen Universitätsklinikum Erlangen: Prof. Rainer Fietkau, Dr. Philipp Schubert, Prof. Markus Hecht (until 30.09.2022) Düsseldorf, Universitätsklinikum: Dr. Balint Tamaskovics, Prof. Wilfried Budach, Dr. Jan Haussmann Frankfurt, Universitätsklinikum: Prof. Claus Rödel, Dr. Maximilian Fleischmann

	Regensburg, Universitätsklinikum: Prof. Oliver Kölbl, Dr. Daniel Heudobler Dresden, BAG/Onkologische Gemeinschaftspraxis: Dr. Thomas Illmer, Dr. Jörgen Radke Bochum, Klinikum der Ruhr-Universität: Prof. Anke Reinacher-Schick, Dr. Linda Wingerter Homburg, Universitätsklinikum des Saarlandes: Dr. Patrick Melchior, Prof. Markus Hecht (after 01.10.2022) Paderborn, Klinik für Hämatologie und Onkologie: Harald Müller-Huesmann, Dr. Attila Salay Magdeburg, Otto von Guericke Universität: Prof. Thomas Brunner, Dr. Peter Hass Klinikum Chemnitz gGmbH: PD Dr. Gunther Klautke, Dr. Frank Vogel	
7	**Study site(s)**	
	1	Universitätsklinikum Erlangen, Strahlenklinik, Universitätsstr. 27, 91054 Erlangen
	2	Universitätsklinikum Düsseldorf, Klinik für Strahlentherapie und Radioonkologie, Moorenstr. 5, 40225 Düsseldorf
	3	Universitätsklinikum Frankfurt, Klinik für Strahlentherapie und Onkologie, Theodor-Stern-Kai 7, 60590 Frankfurt am Main
	4	Universitätsklinikum Regensburg, Klinik und Poliklinik für Strahlentherapie, Franz Josef Strauß Allee 11, 93042 Regensburg
	5	BAG/Onkologische Gemeinschaftspraxis, Arnoldstr. 18, 01307 Dresden
	6	St. Josef Hospital, Klinikum der Ruhr-Universität Bochum, Abt. für Hämatologie, Onkologie und Palliativmedizin Gudrunstr. 56, 44791 Bochum
	7	Universitätsklinikum des Saarlandes, Klinik für Strahlentherapie und Radioonkologie, Kirrberger Str. 100, 66421 Homburg
	8	Brüderkrankenhaus St. Josef Paderborn, Klinik für Hämatologie und Onkologie, Husener Str. 46, 33098 Paderborn
	9	Otto von Guericke Universität Magdeburg, Klinik für Strahlentherapie, Leipziger Str. 44, 39120 Magdeburg
	10	Klinikum Chemnitz gGmbH, Klinik für Radioonkologie, Flemmingstr. 2, 09116 Chemnitz
8	**Publication (reference)**	
	B.F. Tamaskovics, M. Hecht, P. Schubert, et al; 944TiP Randomized phase II study of immune stimulation with pembrolizumab and radiotherapy of recurrent and/or metastatic head and	

	neck squamous cell carcinoma: The IMPORTANCE trial, Annals of Oncology, Volume 34, Supplement 2, 2023 *Schubert P, Tamaskovics B, Haussmann J et al.; Hypofractionated radiotherapy of single tumor lesion increases systemic response rate to pembrolizumab in recurrent or metastatic head-and-neck cancer (R/M-HNSCC): Primary endpoint of the randomized Keynote-717 trial; ESMO 2025 (mini oral presentation)*
9	**Studied period (years): date of first enrolment, date of last completed** **Anmerkung: Hier sollen auch Studienunterbrechungen und vorzeitige Studienbeendigungen/Studienabbrüche unter Angabe der Gründe aufgeführt werden**
	First patient in: 24.07.2018 Last patient out of therapy: 13.06.2024 End of Follow up: 01.10.2024
10	**Phase of development**
	Phase II trial
11	**Objective**
	Primary Objective: Assessment of the effect of local radiotherapy on systemic response to pembrolizumab Local radiotherapy will significantly improve the overall response rate according to iRECIST **Secondary Objective:** Assessment of the effect of local radiotherapy on different response criteria to pembrolizumab: • Response rate according to RECIST • changes of (not irradiated) target lesion • duration of response • progression free survival • overall survival Assessment of safety and tolerability of the combination of pembrolizumab and radiotherapy **Exploratory Objectives:** Assessment of changes of the immunophenotype in peripheral blood after pembrolizumab without and with radiotherapy (longitudinal analysis) Assessment of predictive value of PD-L1 in combination with tumor-infiltrating lymphocytes
12	**Number of patients (planned and analysed)**
	Planned: • Enrolment: 130 Analysed: • 115: Recruitment ended preliminary 31.05.2025

13	**Diagnosis and main criteria for inclusion**
	Diagnosis: • Metastatic HNSCC OR • Locally recurrent HNSCC not suitable for local treatment (at least two lesions, e.g., primary tumor and lymph node) • Progression to first line platinum-based or any second/ third line chemotherapy OR • Progression within 6 months after platinum-based radiochemotherapy of locally advanced disease OR • First line treatment if PD-L1 CPS (combined positive score) ≥1 **Main criteria for inclusion:** • Metastatic HNSCC or metastatic squamous cell CUP (carcinoma of unknown primary) of the neck AND/OR Locally recurrent HNSCC not suitable for curative local treatment within or outside the previously irradiated tissue • At least in one of these lesions must be a need for radiotherapy in near future • Progression after first line platinum-based or any second/ third line chemotherapy OR • Progression within 6 months after platinum-based radiochemotherapy of locally advanced disease OR • First line treatment if PD-L1 CPS (combined positive score) ≥1. (after Amendment 3) • Histological confirmation of HNSCC or squamous cell CUP (carcinoma of unknown primary) of the neck. • At least one measurable lesion according to iRECIST that receives less than 10% of the prescribed dose of the irradiated lesion(s) • ECOG performance status ≤1 • Age ≥ 18 • Written informed consent for the participation in the clinical trial
14	**Test product, dose and mode of administration, batch number**
	Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2.

	Dose and mode of administration Radiotherapy treatment was administered to one, two or three tumor lesions (3Gy per day, total of 36 Gy). Pembrolizumab 200 mg will be administered as 30-minute IV infusion once per every 3 weeks after radiotherapy. Pembrolizumab continued to a maximum of 12 months or till disease progression or unacceptable toxicity. 
15	**Duration of treatment**
	12 months
16	**Reference therapy, dose and mode of administration, batch number**
	Not applicable
17	**Methodology**
	Safety Assessments: Another aim of the trial is the assessment of safety and tolerability of the combination of pembrolizumab and radiotherapy. Toxicity will be documented according to CTCAE v4.0 before every administration of pembrolizumab. The trial focuses both on the overall toxicity grade 3 or higher and on some special subsets. Both radiotherapy and pembrolizumab can cause pneumonitis. Consequently, pneumonitis grade 2 and pneumonitis grade 3 or higher will be compared separately in both arms. Pembrolizumab may also increase the severity of radiation dermatitis. Thus, skin toxicity is also evaluated separately as grade 2 toxicity and as grade 3 or higher toxicity in both arms.

Efficacy Assessments:

The primary efficacy endpoint is the rate of patients achieving CR or PR as best response during/after treatment overall response rate (ORR) according to iRECIST. The irradiated tumor lesion(s) will be excluded from the iRECIST evaluation. The response rate according to RECIST 1.1 criteria is a secondary endpoint of the trial.

Sample Size Calculation

Based on published results, the ORR after standard pembrolizumab therapy is assumed to be around 18%. The doubling of this ORR to 36% by adding radiotherapy seems to be a reasonable aim, and is unequivocally considered to be a major, clinically relevant advantage. In order not to miss such a distinct signal for improvement by the experimental treatment (if it actually exists) with a high level of confidence (power = 80%), 65 evaluable patients per arm, i.e., a total of n = 130, have to be observed, based on an alpha error rate of 0.1 (one-sided). The comparatively high alpha error level of 10% is acceptable within the framework of a phase II study.

18 **Results**

Patient characteristics

Recruitment to the study started in July 2018, and was closed in May 2024. Data base lock for this final analysis was January 2024. A total of 115 patients from a total of eight different study sites were randomized into the trial. The average and median documented duration of follow-up since randomisation is 12.5 and 9.3 months, respectively, ranging up to 58.7 months, and quite similar in both study arms.

At its final closure, the database included information on all 115 randomized, evaluable patients, 57 in **arm A (experimental arm with radiotherapy)** and 58 in **arm B (control, or standard arm)**, forming the ITT full analysis set. Fifteen eligible patients (13%) without having received the protocol-defined radiotherapy dose (arm A) and/or without having received at least two cycles of pembrolizumab according to the protocol were excluded from the per-protocol (PP) population. Due to this comparatively high proportion, and the fact that most of these drop-outs occurred in the experimental arm, the results of the PP-based efficacy analyses have to be interpreted with caution.

The safety analysis is based on a population of 110 patients.

The distribution of age and gender shows a slight tendency to more elderly, and female patients in the experimental arm.

Parameter / age cohort	arm A	arm B	Total
n	57	58	115
Mean ± SD	66.7 ± 9.9	62.8 ± 9.2	64.7 ± 9.7
Median	67	63	66
Quartile	61 - 74	57 - 68.8	58 - 72
Range	34 - 80	39 - 88	34 - 88
< 50 y	2 (4%)	3 (5%)	5 (4%)
50 - 59 y	10 (18%)	17 (29%)	27 (23%)
60 - 69 y	18 (32%)	25 (43%)	43 (37%)
70 - 79 y	24 (42%)	10 (17%)	34 (30%)
>=80 y	3 (5%)	3 (5%)	6 (5%)

Category	arm A	arm B	Total
n	57	58	115
Male	48 (84%)	54 (93%)	102 (89%)
Female	9 (16%)	4 (7%)	13 (11%)

Presumably due to some incorrect reporting of stratum at randomization, the ECOG performance status (as reported at the screening visit), is slightly less favorable in arm A.

Score	arm A	arm B	Total
n	57	58	115
ECOG 0	12 (21%)	17 (29%)	29 (25%)
ECOG 1	45 (79%)	41 (71%)	86 (75%)

Smoking status was rather well balanced. The majority of the patients were previous smokers.

Category	arm A	arm B	Total
n	57	58	115
Non-smoker	12 (21%)	10 (17%)	22 (19%)
Previous smoker	36 (63%)	32 (55%)	68 (59%)
Smoker	9 (16%)	16 (28%)	25 (22%)

Almost all patients were recorded as having experienced “any relevant concomitant diseases”.

Category	arm A	arm B	Total
n	57	58	115
Yes	49 (86%)	54 (93%)	103 (90%)
No	2 (4%)	1 (2%)	3 (3%)
Missing information	6 (11%)	3 (5%)	9 (8%)

Primary Diagnosis of Head and Neck Cancer

The median time between initial diagnosis of head and neck cancer and entrance into the study amounted to about one year, with good balance between the study arms.

Parameter	arm A	arm B	Total
n	57	58	115
Mean ± SD	22.3 ± 37	25.8 ± 33.8	24.1 ± 35.3
Median	11.7	13.4	13
Quartile	5.7 - 22.9	7.5 - 34.4	7.2 - 23.5
Range	0.3 - 265	1.1 - 204.1	0.3 - 265

A rather broad distribution of the primary tumor locations has been shown, which is rather similar in both arms.

Localisation	arm A	arm B	Total
n	57	58	115
Oral cavity	16 (28%)	15 (26%)	31 (27%)
Oropharynx	21 (37%)	26 (45%)	47 (41%)
Hypopharynx	15 (26%)	17 (29%)	32 (28%)
Larynx	11 (19%)	5 (9%)	16 (14%)
Nasopharynx	1 (2%)	--	1 (1%)
CUP	1 (2%)	3 (5%)	4 (3%)

A known positive p16 status was reported in a minority of the patients only.

Category	arm A	arm B	Total
n	57	58	115
Negative	26 (46%)	31 (53%)	57 (50%)
Positive	7 (12%)	12 (21%)	19 (17%)
Unknown	24 (42%)	15 (26%)	39 (34%)

T and N staging exhibit a large variability of findings at the time of the initial diagnosis of head and neck cancer, with distant metastases (M) present in only 21% of the patients. The frequency of undifferentiated tumors showed a rather good balance between the randomisation arms. Information on the L and V category were generally not provided.

Category	arm A	arm B	Total
n	57	58	115
T1	8 (14%)	8 (14%)	16 (14%)
T2	15 (26%)	15 (26%)	30 (26%)
T3	11 (19%)	8 (14%)	19 (17%)
T4	19 (33%)	22 (38%)	41 (36%)
No information	4 (7%)	5 (9%)	9 (8%)

Category	arm A	arm B	Total
n	57	58	115
N0	11 (19%)	13 (22%)	24 (21%)
N1	5 (9%)	6 (10%)	11 (10%)
N2	23 (40%)	23 (40%)	46 (40%)
N3	17 (30%)	15 (26%)	32 (28%)
Nx	--	1 (2%)	1 (1%)
No information	1 (2%)	--	1 (1%)

Category	arm A	arm B	Total
n	57	58	115
M0	44 (77%)	47 (81%)	91 (79%)
M1	13 (23%)	11 (19%)	24 (21%)

Organ	arm A	arm B	Total
n	57	58	115
Lung	11 (19%)	7 (12%)	18 (16%)
Liver	2 (4%)	3 (5%)	5 (4%)
CNS	--	--	--
Skin	--	--	--
Other	3 (5%)	5 (9%)	8 (7%)

Category	arm A	arm B	Total
n	57	58	115
G1	2 (4%)	2 (3%)	4 (3%)
G2	22 (39%)	29 (50%)	51 (44%)
G3	23 (40%)	20 (34%)	43 (37%)
No information	10 (18%)	7 (12%)	17 (15%)

After the primary diagnosis, surgery was performed in about half of the patients, with R0 results in 39%, i.e., in 76% of the patients who underwent resection.

Category	arm A	arm B	Total
n	57	58	115
R0	21 (37%)	24 (41%)	45 (39%)
R1	4 (7%)	4 (7%)	8 (7%)
R2	1 (2%)	--	1 (1%)
Rx	3 (5%)	2 (3%)	5 (4%)
No surgery	28 (49%)	27 (47%)	55 (48%)
No information	--	1 (2%)	1 (1%)

The vast majority had undergone previous surgery, irradiation and/or chemotherapy as tumor pre-treatment. All pre-treatment types were equally distributed among the randomized groups.

Treatment	arm A	arm B	Total
n	57	58	115
No previous therapy	2 (4%)	2 (3%)	4 (3%)
Surgery	42 (74%)	43 (74%)	85 (74%)
Chemotherapy	45 (79%)	46 (79%)	91 (79%)
Radiotherapy	51 (89%)	50 (86%)	101 (88%)
Other	4 (7%)	4 (7%)	8 (7%)

Treatment parameters and feasibility analysis

PROTOCOL TREATMENT – PEMBROLIZUMAB

Overall, 813 pembrolizumab administrations were documented, 381 in arm A and 432 in arm B. The number of administered pembrolizumab cycles per patient is presented in the table below. The amount of the antibody received is rather equal in both arms. No pembrolizumab was given in 5 patients (5/115, 4%), three in arm A (3/57, 5%) and two in arm B (3/58, 3%), respectively.

	arm A	arm B	Total
n	57	58	115
Mean ± SD	6.7 ± 6	7.4 ± 6.3	7.1 ± 6.1
Median	4	5	5
Quartile	2 - 11	2 - 11	2 - 11
Range	0 - 18	0 - 18	0 – 18

15 (15/115, 13%) patients did not receive the projected amount of at least two cycles of pembrolizumab, distinctly more patients in the radiotherapy arm (11/57, 19%) compared to arm B (4/58, 7%).

The duration of pembrolizumab treatment in the patients receiving the antibody was similar in both study arms. The proportion of delayed pembrolizumab applications was 7%, almost

identical in both arms. In about half of the patients, no delay of application occurred. However, slightly more patients in arm A had a deviation from the protocol time schedule.

PROTOCOL TREATMENT – RADIOTHERAPY IN THE EXPERIMENTAL ARM

Out of the 57 patients in the experimental arm, three did definitively not receive any radiotherapy. In another patient, who died 4 weeks after randomization, no data on the amount of radiotherapy were provided.

The median duration of radiotherapy amounted to 16 days, which likewise was the exact duration in more than half of the patients. Another 23% had a duration of 17 days.
In all but 5 patients 12 fractions were applied, while all but 4 patients received a total dose of 36 Gy, corresponding to the protocol plan, including the patient with 25 fractions. In three patients, a premature termination of the radiotherapy was reported. The reasons were death, poor performance status with transfer to an intensive care unit, and patient's wish, respectively.
Thus, based on the total ITT population of the experimental arm, 49/57 patients (86%) received the full dose required by the protocol. Only these qualify for the per-protocol population.

END OF PROTOCOL TREATMENT

Only 27% of the patients underwent the full course of pembrolizumab treatment according to the protocol, i.e., for 12 months (according to the original protocol) or two cycles (according to the protocol amendment). The predominant reasons for early termination were progressive disease or death (both slightly more common in the control arm). All other causes occurred only rarely.

Reason for (premature) termination	arm A	arm B	Total
n	57	58	115
After 12 months (regular)	8 (14%)	12 (21%)	20 (17%)
After 2 cycles of pembrolizumab (regular)	7 (12%)	4 (7%)	11 (10%)
Progression	22 (39%)	26 (45%)	48 (42%)
Death	9 (16%)	11 (19%)	20 (17%)
Unacceptable toxicity	4 (7%)	1 (2%)	5 (4%)
Other AE/SAE	3 (5%)	1 (2%)	4 (3%)
Patient's wish	4 (7%)	2 (3%)	6 (5%)
Missing documentation*	--	1 (2%)	1 (1%)

END OF STUDY

The reasons for terminating the participation in the study are provided in table below. They show a virtually similar distribution among the study arms. For three patients no end-of-study record exists.

Death is the prominent cause for the end of observation, in more than two thirds of the patients.

In 81% of the 79 deceased patients, the cause was the underlying cancer disease. No fatal event was reported to be caused by protocol treatment toxicity. Details on the "other"

reasons are frequently unknown, but include multi-organ failure, dislocated tracheal cannula, covid infection, bleeding, surgery, or lung infections.

Reason	arm A	arm B	Total
n	56	56	112
According to protocol (after 12 months of follow-up)	9 (16%)	10 (18%)	19 (17%)
According to protocol (after safety follow-up)	4 (7%)	3 (5%)	7 (6%)
Death during the protocol treatment phase	10 (18%)	10 (18%)	20 (18%)
Death during the follow-up period	29 (52%)	30 (54%)	59 (53%)
Patient's wish	3 (5%)	1 (2%)	4 (4%)
Lost to follow-up	1 (2%)	2 (4%)	3 (3%)

Category	arm A	arm B	Total
n	39	40	79
Death due to cancer	32 (82%)	32 (80%)	64 (81%)
Death due to other reasons than cancer or toxicity	7 (18%)	8 (20%)	15 (19%)

TUMOR RESPONSE AT THE INITIAL STAGING VISIT REQUIRED BY THE PROTOCOL

Tumor response according to iRECIST at the protocol-defined first restaging visit is available in 77 patients, i.e., in only 67% of the randomized ITT population. The response categories and the corresponding overall objective response rate (ORR) observed are shown in the table below for the non-irradiated lesions and for the irradiated lesions in the experimental arm. In this subgroup, objective responses of non-irradiated lesions were more frequent in arm A (21%, 95% confidence interval [CI]: 9 - 36%) than in arm B (8%, 95% CI: 2 - 21%) (Odds ratio [OR]: 3.01; p = 0.10, Fisher's exact text, one-sided).

Response (iRECIST) at 1st restaging					
non-irradiated lesions	arm A	arm B	Total	irradiated lesions	arm A
n	39	38	77	n	39
iCR	2 (5%)	--	2 (3%)	iCR	1 (3%)
iPR	6 (15%)	3 (8%)	9 (12%)	iPR	8 (21%)
iSD	11 (28%)	11 (29%)	22 (29%)	iSD	24 (62%)
iPD, confirmed	0 (0%)	0 (0%)	0 (0%)	iPD, confirmed	--
iPD, unconfirmed	20 (51%)	22 (58%)	42 (55%)	iPD, unconfirmed	4 (10%)
Missing iRECIST result	--	2 (5%)	2 (3%)	Missing iRECIST result	2 (5%)
iCR + iPR *	8 (21%)	3 (8%)	11 (14%)	iCR + iPR	9 (23%)

* p = 0.10, Fisher's exact test, one-sided

OVERALL BEST TUMOR RESPONSE (IRECIST), PRIMARY ENDPOINT

The overall best objective response, defined as achieving a CR or PR category during protocol treatment, is the primary endpoint, with a one-sided significance level of $p < 0.1$ required for a positive signal of superior efficacy in this randomized phase II study, an improvement from 18% to 36% in the overall response rate (ORR) was anticipated at the planning stage of the protocol. The table displays the best response categories observed as well as the proportion with CR + PR. The latter results correspond quite well to the anticipated rates.

In spite of the lower patient number (compared to the initial sample size calculation of n = 130), a significant p value of 0.097 is obtained. The OR amounts to 1.87 with lower

boundaries of one-sided 95% and 90% confidence intervals of 0.097 and 1.01, respectively. The latter corresponds to the primary endpoint analysis, excluding an OR of 1.0. The absolute rate difference for objective response between the arms is +12.7%, with lower boundaries of one-sided 95% and 90% confidence intervals of -1.1% and +2.0%, respectively. A stratified test adjusting for the stratification factors ECOG status and M status at baseline returns a slightly higher p value: p = 0.12, Mantel-Haenszel test with continuity correction, one-sided.

Best response (iRECIST), non-irradiated lesions (ITT population)	**arm A**	**arm B**	**Total**
n	57	58	115
iCR	6 (11%)	3 (5%)	9 (8%)
iPR	14 (25%)	10 (17%)	24 (21%)
iSD	9 (16%)	10 (17%)	19 (17%)
iPD, confirmed	6 (11%)	10 (17%)	16 (14%)
iPD, unconfirmed	12 (21%)	11 (19%)	23 (20%)
Missing iRECIST result	--	3 (5%)	3 (3%)
No restaging	10 (18%)	11 (19%)	21 (18%)
iCR + iPR*	20 (35%)	13 (22%)	33 (29%)
95% CI	23 – 49%	13 – 35%	

* p = 0.097, Fisher's exact test, one-sided

In addition, the corresponding results for the per-protocol population presents a somewhat larger estimate of 19.4% for the ORR difference (lower boundary of one-sided 95% CI: +4.0%; OR = 2.43, lower 95% CI: 1.19; p = 0.033, Fisher's exact test, one-sided). The best response (iRECIST) of the irradiated lesions in arm A shows an ORR rather similar to the non-irradiated lesions in the radiotherapy group.

Best response (iRECIST), non-irradiated lesions (PP population)	**arm A**	**arm B**	**Total**
n	46	54	100
iCR	6 (13%)	3 (6%)	9 (9%)
iPR	14 (30%)	10 (19%)	24 (24%)
iSD	9 (20%)	10 (19%)	19 (19%)
iPD, confirmed	5 (11%)	10 (19%)	15 (15%)
iPD, unconfirmed	10 (22%)	10 (19%)	20 (20%)
Missing iRECIST result	--	3 (6%)	3 (3%)
No restaging	2 (4%)	8 (15%)	10 (10%)
iCR + iPR*	20 (43%)	13 (24%)	33 (33%)

* p = 0.033, Fisher's exact test, one-sided

OVERALL BEST TUMOR RESPONSE (RECIST)

The corresponding results for the RECIST evaluation are quite similar to those for iRECIST, with a slightly smaller difference between the groups.

Best response (RECIST), non-irradiated lesions	**arm A**	**arm B**	**Total**	**irradiated lesions**	**arm A**
n	57	58	115	n	57
CR	6 (11%)	3 (5%)	9 (8%)	CR	7 (12%)
PR	13 (23%)	11 (19%)	24 (21%)	PR	15 (26%)
SD	9 (16%)	11 (19%)	20 (17%)	SD	21 (37%)
PD	19 (33%)	21 (36%)	40 (35%)	PD	3 (5%)
Missing iRECIST result	--	1 (2%)	1 (1%)	Missing iRECIST result	1 (2%)
No restaging	10 (18%)	11 (19%)	21 (18%)	No restaging	10 (18%)
CR + PR*	19 (33%)	14 (24%)	33 (29%)	CR + PR	22 (39%)
95% CI	21 – 47%	14 – 37%			

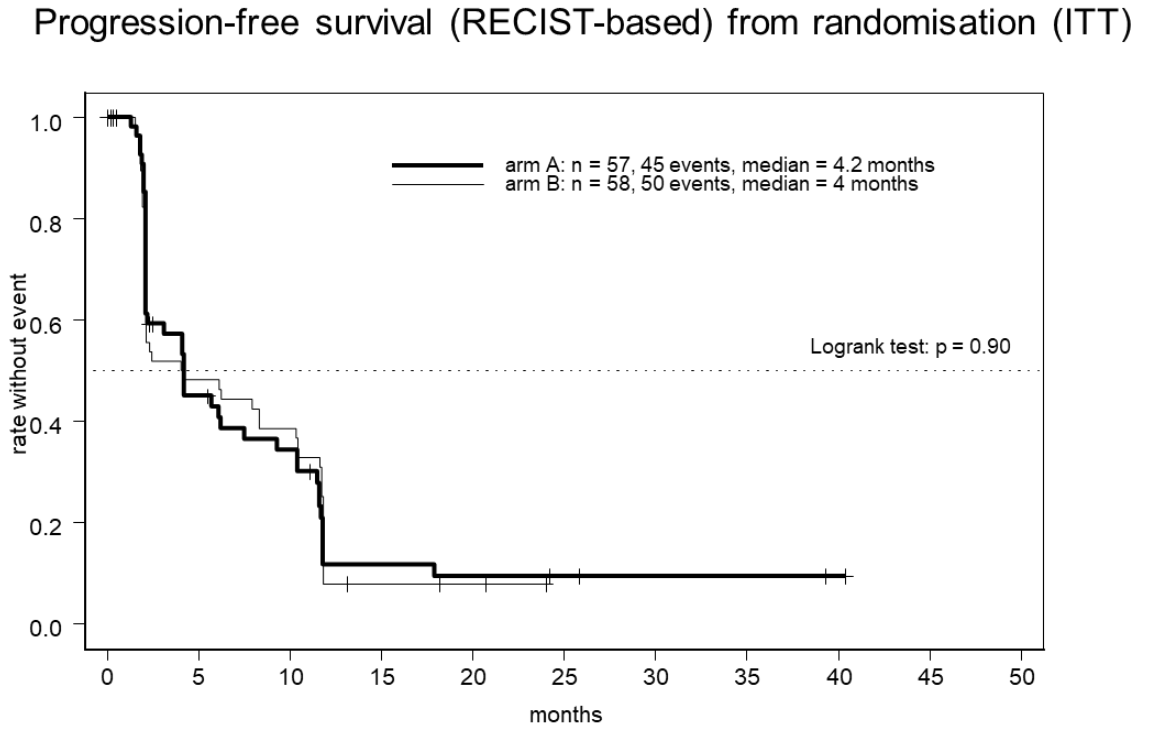
* p = 0.19, Fisher's exact test, one-sided

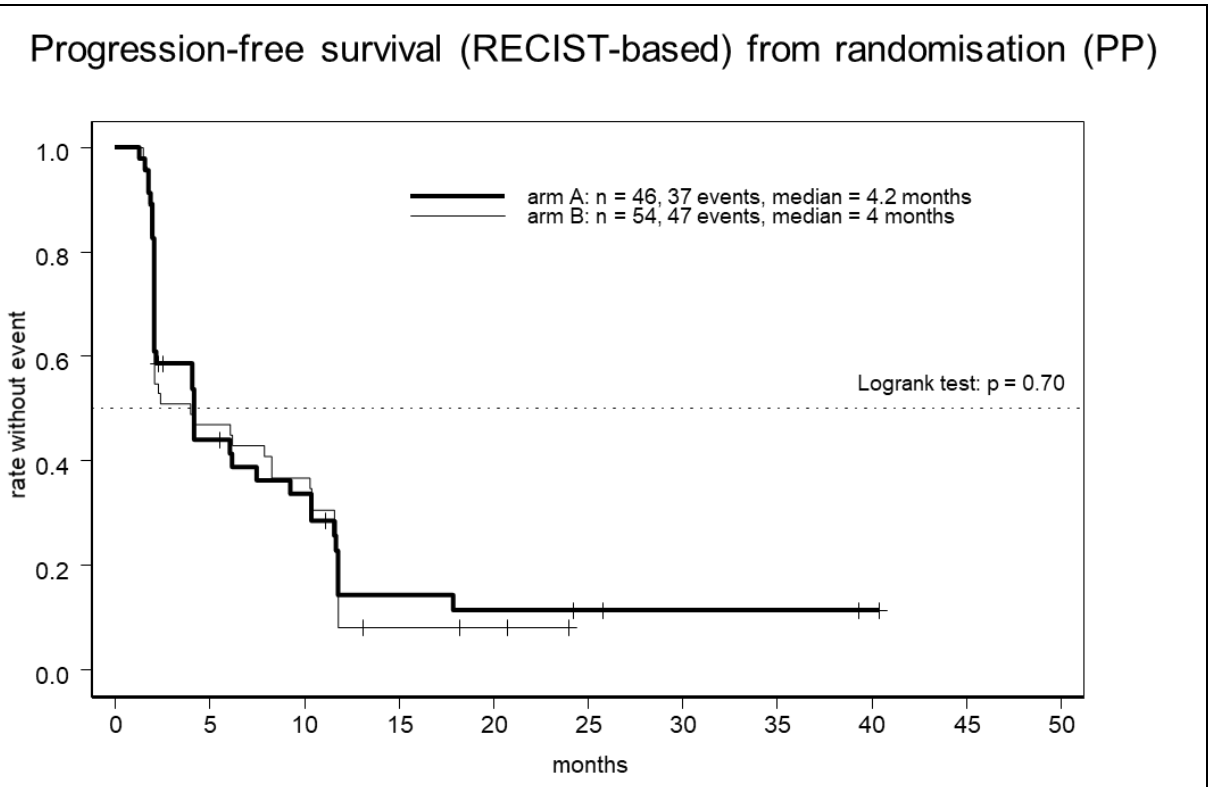
PROGRESSION-FREE SURVIVAL (PFS)

The Kaplan-Meier estimation of progression-free survival (PFS) from the time point of randomization, based on RECIST evaluation is provided in the figure below, based on a total of 95 observed PFS events in the ITT population of 115 patients (83%). It shows no relevant difference between the arms (p = 0.90, log rank test). The medians in arm A and B are quite similar, with 4.2 months in arm A (95% CI: 2.1 – 10.4) and 4.0 months in arm B (95% CI: 2.1 – 10.4), respectively. The 6-month PFS rates estimated according to Kaplan-Meier are 43% (95% CI: 31 - 59%) and 48% (95% CI: 37 - 63%), respectively.

The hazard ratio (HR) derived from a Cox model with the control arm as reference amounts to HR = 0.96 (95% CI: 0.64 – 1.43), likewise suggesting no relevant difference between the arms.

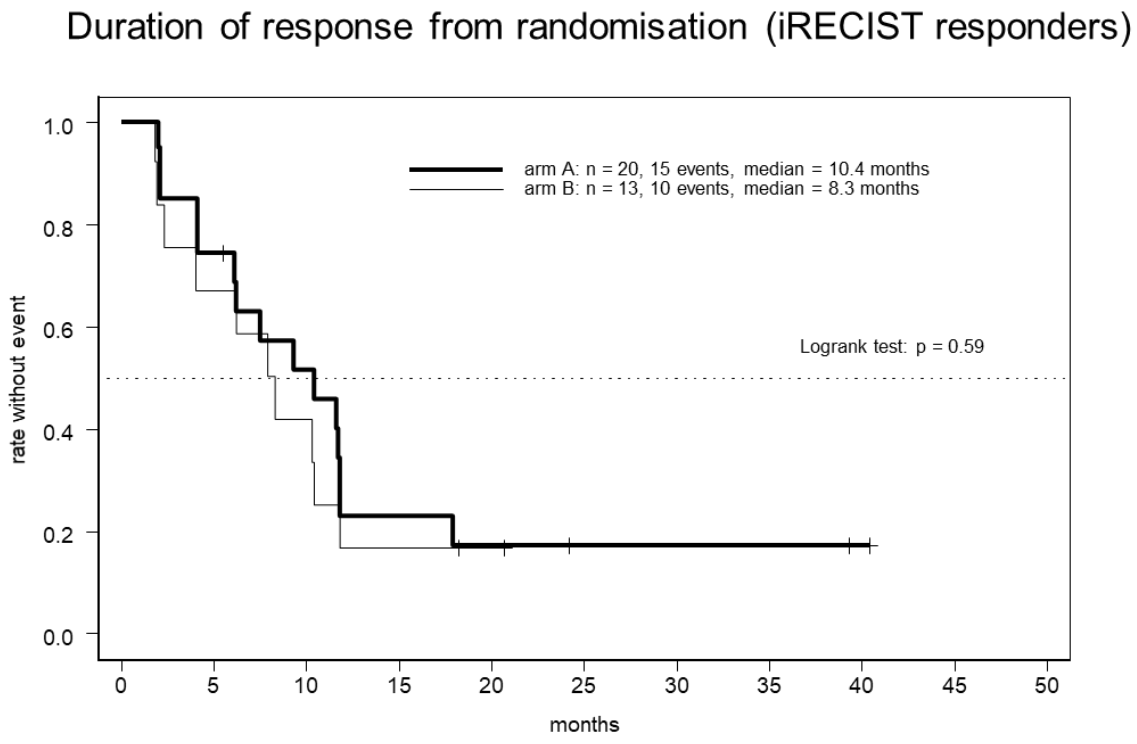
The corresponding per-protocol analysis, based on a total of 84 events in 100 qualifying patients results in an almost unchanged output (p = 0.70; HR = 0.91 (95% CI: 0.59 – 1.40).





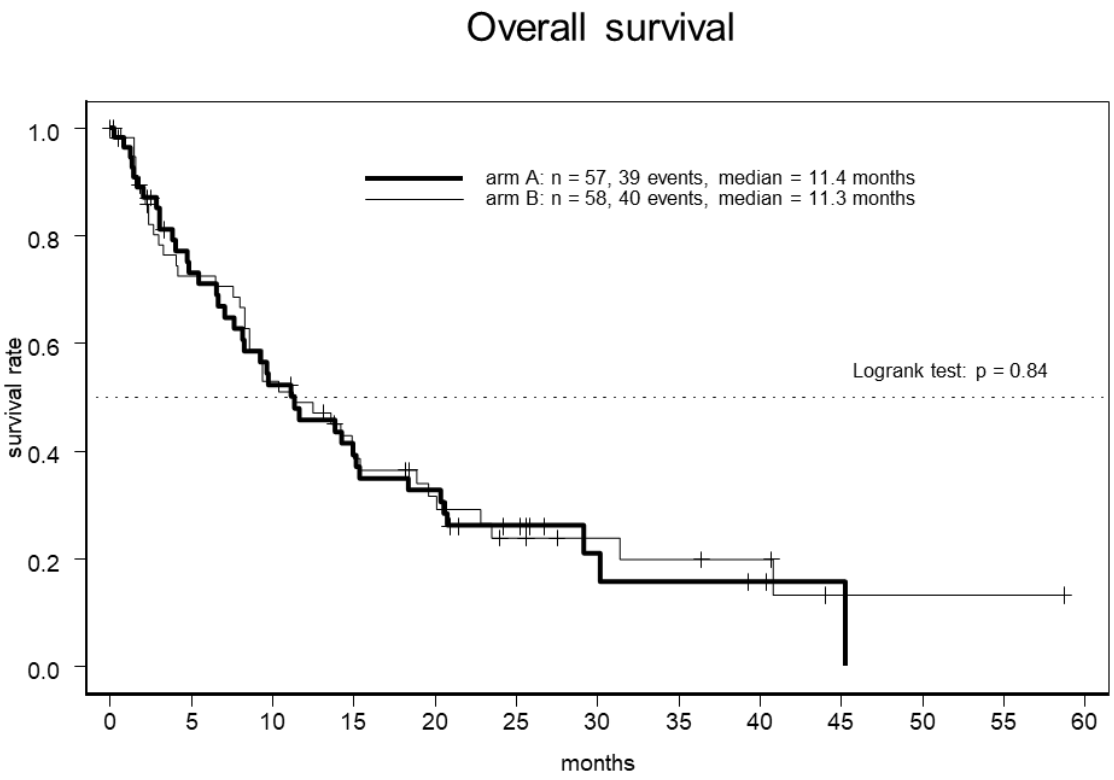
DURATION OF RESPONSE

The duration of response, defined as the time from randomization to the detection of RECIST-defined progressive disease (or censoring) in the subgroup of patients achieving CR or PR (primary endpoint definition), shows no relevant differences between the study groups can be discerned (p = 0.59, log rank test). It amounts to more than 8 months in the majority of the responding patients.



OVERALL SURVIVAL

The Kaplan-Meier estimation of overall survival (OS) from the time point of randomization, based on a total of as yet 79 observed deaths in the ITT population of 115 patients (69%) is presented in the figure below with virtually superimposable curves. The medians in arm A and B are almost identical with 11.4 (95% CI: 8.2 – 18.4) and 11.3 months (95% CI: 8.6 – 19.6), respectively. The hazard ratio (HR) derived from a Cox model amounts to HR = 1.04 (95% CI: 0.67 – 1.63).



Safety analyses

An overview presents observed adverse events (AE), overall and according to severity and other pre-defined categories. At least one event was recorded in almost all patients, and at least one severe event in more than 60%. Overall, adverse events did not seem to occur more commonly in the radiotherapy arm.

Adverse events were recorded and graded according to NCI-CTCAE V.4, with individual items sorted to 22 system organ classes (SOC).

For arm A and for arm B a table shows the incidence and severity of AEs, based on the maximum severity grade observed by patient and by CTCAE category during the total course of study treatment, without considering the investigator's assessment on causality. A broad variety of events was observed in both study arms, while only few categories had an incidence of more than 20%. In either arm, anemia, fatigue, pain, gastrointestinal disorders, infections, dizziness, dyspnea, and skin reactions were quite frequent. Dermatitis due to radiation occurred in 19% of the patients and was generally mild.

One event record without appropriate CTCAE category was recorded in arm A: "stuffy nose", severity grade 1.

Parameter	Arm A	Arm B
n (patients)	54	56
Total number of adverse events reported	562	639
Total number of serious adverse events reported	47	52
Number of adverse events of severity grade 3 to 5	68	78
Number of patients with any adverse event reported	53 (98%)	55 (98%)
Number of patients with any AE of severity grade 3 to 5	33 (61%)	35 (63%)
Number of patients with any adverse event, reported as related to protocol therapy	38 (70%)	35 (63%)
Number of patients with any AE of severity grade 3 to 5, reported as related to protocol therapy	6 (11%)	3 (5%)
Number of patients with any serious AE (SAE)	26 (48%)	32 (57%)
Number of patients with any serious AE (SAE) , reported as related to protocol therapy	8 (15%)	4 (7%)

QUALITY OF LIFE

Functional scales

The EORTC QLQ-C30 was to be filled by the patients at the screening visit and before the 3rd and 7th application of pembrolizumab. While the questionnaire is available in 112 patients at the beginning, only about half of the patients filled the form at the following visits, rather similar in both arms. Due to this continuous loss process over time, and the resulting (presumably positive) selection bias, a comparison between the visits is difficult to interpret. However, there seems to be no deterioration of functioning during continued protocol therapy, in both treatment arms.

Symptom scales / items

Fatigue is the most prominent symptom. No major differences between the arms can be detected, albeit some scales indicate a slightly favorable trend in arm A, and possibly AE-related.

Global health status /QoL

At screening, the global health status is clearly impaired, with a median value of 50, similar in both randomization groups. Any negative effect of the radiotherapy cannot be discerned.

Overall Feasibility

The combination of pembrolizumab and local radiotherapy proved to be feasible in a multicentre setting. The majority of patients in the experimental arm (86%) received the full protocol-defined radiotherapy dose of 36 Gy, and more than 80% of all randomized patients received at least two cycles of pembrolizumab. Thus, the essential study treatments could be delivered as planned in most cases.

Nevertheless, some challenges were observed. In the experimental arm, a higher proportion of patients failed to receive the minimum planned systemic therapy compared to the control

	arm (19% vs. 7%). Delays or deviations in pembrolizumab administration occurred in about 7% of applications, which was similar between the arms. Taken together, the study regimen was implementable in daily clinical practice, but the high rate of early treatment discontinuation reflects the aggressive natural course of metastatic HNSCC rather than protocol-related limitations.
19	**Summary – Conclusions**
	This multicentre, randomized, open-label phase II trial investigated the addition of local radiotherapy to pembrolizumab in patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC). A total of 115 patients were enrolled across several sites and randomized to receive either pembrolizumab plus local radiotherapy (Arm A) or pembrolizumab alone (Arm B). The majority of patients in the experimental arm received the full planned radiotherapy dose, and treatment with pembrolizumab was generally feasible, although early discontinuation was frequent due to disease progression. The primary endpoint, overall response rate (ORR) according to iRECIST in non-irradiated lesions, showed a higher response rate in the experimental arm compared to the control arm, reaching the predefined statistical significance threshold for this phase II design. Secondary endpoints, including ORR by RECIST 1.1, progression-free survival (PFS), and overall survival (OS), demonstrated no relevant differences between treatment arms. Safety analyses confirmed that the combination of pembrolizumab and radiotherapy was well tolerated, with adverse events largely consistent with the known safety profile of each treatment modality. No unexpected safety signals or treatment-related deaths occurred. Quality-of-life assessments did not indicate deterioration during treatment, although interpretation was limited by incomplete data collection. **Conclusions** • The combination of local radiotherapy with pembrolizumab in recurrent/metastatic HNSCC is feasible and safe. • A significant improvement in objective response rate was observed, but no benefit in PFS or OS. The study supports the biological rationale for combining radiotherapy with immunotherapy, but highlights the need for further prospective trials with larger sample size and refined patient selection.
20	**Date of report**
	24 Sept 2025