Induction chemoimmunotherapy followed by CD8+ immune cell-based patient selection for chemotherapy-free radioimmunotherapy in locally advanced head and neck cancer

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ABSTRACT

Purpose The first aim of the trial is to study feasibility of combined programmed death protein ligand 1/cytotoxic T-lymphocyte-associated protein 4 inhibition concomitant to radiotherapy. In addition, efficacy of the entire treatment scheme consisting of induction chemoimmunotherapy followed by chemotherapy-free radioimmunotherapy (RIT) after intratumoral CD8 +immune cell-based patient selection will be analyzed.

Methods Patients with stage III–IVB head and neck squamous cell carcinoma were eligible for this multicenter phase II trial. Treatment consisted of a single cycle of cisplatin 30 mg/m² days 1–3, docetaxel 75 mg/m² day 1, durvalumab 1500 mg fix dose day 5 and tremelimumab 75 mg fix dose day 5. Patients with increased intratumoral CD8 +immune cell density or pathological complete response (pCR) in the rebiopsy entered RIT up to a total dose of 70 Gy. Patients received further three cycles of durvalumab/tremelimumab followed by eight cycles of durvalumab mono (every 4 weeks). The intended treatment for patients not meeting these criteria was standard radiochemotherapy outside the trial. Primary endpoint was a feasibility rate of patients entering RIT to receive treatment until at least cycle 6 of immunotherapy of ≥80%.

Results Between September 2018 and May 2020, 80 patients were enrolled (one excluded). Out of these, 23 patients had human papilloma virus (HPV)-positive oropharyngeal cancer. Median follow-up was 17.2 months. After induction chemoimmunotherapy 41 patients had pCR and 31 had increased intratumoral CD8 +immune cells. Of 60 patients entering RIT (primary endpoint cohort), 10 experienced limiting toxic (mainly hepatitis) and four discontinued for other reasons, resulting in a feasibility rate of 82%. The RIT cohort (n=60) had a progression-free survival (PFS) rate at one and 2 years of 78% and 72%, respectively, and an overall survival rate at one and 2 years of 90% and 84%, respectively. Patients with HPV-positive oropharyngeal cancers had greater benefit from RIT with

a 2-year PFS rate of 94% compared with 64% for HPV-negative oropharyngeal cancers and other locations. In the entire study cohort (n=79) the 2-year PFS rate was 68% (91% for HPV-positive oropharynx vs 59% for others). Toxicity grade 3–4 mainly consisted of dysphagia (53%), leukopenia (52%) and infections (32%).

Conclusions The trial met the primary endpoint feasibility of RIT. Induction chemo-immunotherapy followed by chemotherapy-free RIT after intratumoral CD8 +immune cell-based patient selection has promising PFS.

Trial registration number The trial was registered with ClinicalTrials.gov (identifier: NCT03426657). The trial was conducted as investigator-sponsored trial (IST).

INTRODUCTION

Immune checkpoint inhibitors targeting the programmed death protein 1 (PD-1)/programmed death protein ligand 1 (PD-L1) pathway are first line treatment in recurrent and/or metastatic head and neck squamous cell carcinoma (HNSCC).^{1,2}

Two randomized phase III trials studied the combination of radiochemotherapy with PD-1/PD-L1 pathway blockade in locally advanced HNSCC.^{3,4} While the results of the Keynote-412 trial are still pending, the Javelin Head and Neck 100 trial was negative regarding its primary endpoint progression-free survival (PFS).⁵

Another treatment strategy for laryngeal and hypopharyngeal cancer is the sequential administration of induction chemotherapy and radio(chemo)therapy,^{6,7} whereas this treatment scheme did not improve survival compared with radiochemotherapy alone.⁸

Nevertheless, induction chemotherapy is still under investigation as method for patient selection for radiotherapy de-escalation strategies.^{9,10}

In the CheckRad-CD8 trial a single cycle of induction chemoimmunotherapy is administered to select patients for a further chemotherapy-free radioimmunotherapy (RIT). The concomitant administration of the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antagonist was chosen due to its synergistic immunological effects with radiotherapy, which can be further enhanced by PD-1/PD-L1 pathway blockade in preclinical models.¹¹ HNSCC is probably an appropriate tumor entity for immune checkpoint inhibition due to its high immune cell infiltration and PD-L1 expression, which is even higher in human papilloma virus (HPV) induced tumors.^{12,13} In the phase II CONDOR trial, both durvalumab and the combination of durvalumab and tremelimumab showed efficacy even in PD-L1 low/negative recurrent and/or metastatic HNSCC.¹⁴ A recent phase I trial also indicated a synergistic antitumor activity of the CTLA-4 antagonist ipilimumab and radiotherapy.¹⁵

The current analysis of the primary endpoint of the CheckRad-CD8 trial is the first report on feasibility and efficacy of a RIT with combined targeting of both PD-L1 and CTLA-4 immune checkpoints in locally advanced HNSCC.

MATERIAL AND METHODS

Trial design and treatment

CheckRad-CD8 is a single-arm multicenter phase II study. Treatment consisted of a single cycle of cisplatin 30 mg/m² days 1–3, docetaxel 75 mg/m² day 1, durvalumab 1500 mg fix dose day 5 and tremelimumab 75 mg fix dose day 5. Patients with increased intratumoral CD8 +immune cell density or pathological complete response (pCR) in the rebiopsy entered RIT. Radiotherapy was performed in standard fractionation (5 days per week) using a simultaneous integrated boost concept. A cumulative dose of 70.0/63.0/54.0 Gy was delivered in 35 fractions by intensity modulated radiation therapy to the gross tumor volume, involved lymph node levels and elective lymph node levels, respectively. Patients received further three cycles of durvalumab/tremelimumab followed by eight cycles of durvalumab mono (every 4 weeks). The intended treatment for patients not meeting these criteria was standard radiochemotherapy outside the trial. More detailed information on the trial design has previously been reported.¹⁶

Patients

Eligible patients had histologically confirmed HNSCC stage III–IVB (according to the TNM Classification of Malignant Tumors (TNM) eighth edition) of the oral cavity, oropharynx, hypopharynx or supraglottic larynx. More details on inclusion and exclusion criteria have previously been reported.¹⁶

Endpoints and assessments

The primary endpoint of the CheckRad-CD8 trial is feasibility of combined PD-L1/CTLA-4 inhibition concomitant

to radiotherapy. A feasibility rate of patients entering RIT (primary endpoint cohort) to receive treatment until at least cycle 6 of immunotherapy of ≥80% is expected. The acceptance of a feasibility rate of ≥80% bases on maximum tolerable dose definitions of phase I trials in oncology.¹⁷ Toxicity was scored according to the Common Terminology Criteria for Adverse Events (V.4.03). Key secondary endpoints included PFS and overall survival (OS). OS was defined as the time from study inclusion to the date of death from any cause. PFS was defined as time from study inclusion to the date of disease progression or death. Disease progression is assumed in case of locoregional progression or distant metastases identified by imaging, biopsy or salvage surgery of the primary tumor with pathological evidence of viable tumor after RIT and neck dissection >20 weeks from the end of RIT with pathological evidence of viable tumor. A neck dissection with pathological evidence of residual viable tumor performed ≤20 weeks from the end of radiochemotherapy is considered as part of the treatment scheme and not rated as PFS event according to the definition in the most recent phase III trials.^{3,4}

Biomarker analyses

CD8 (C8/144B, 1:100) and PD-L1 (Ventana SP263 assay) immunohistochemistry was performed on a Ventana Benchmark Ultra autostainer according to accredited staining protocols (<https://www.dakks.de/en>). PD-L1 was scored according to the durvalumab-linked PD-L1 scoring algorithm ($TC_{area}\text{-score}[\%] = \text{positive tumor cell area per total tumor cell area}$; $IC_{area}\text{-score}[\%] = \text{proportion of the area occupied by PD-L1 positive tumor associated IC per total area occupied by tumor-associated IC}$). Whole slides stained for CD8 were digitalized (P250 slide scanner, 3DHitech), and CD8 infiltration was detected quantitatively (per mm² intratumoral (tumor cell area), in the tumor associated stroma and in the total tumor area using QuPath v0.2.0. Details were described previously.^{16,18}

Whole blood samples of the patients collected at study inclusion were analyzed with multi-color flow cytometry according to previously published and clinically applied immunophenotypin protocols.^{16,19}

Statistical analysis

Primary endpoint was the feasibility rate of patients entering RIT to receive treatment until at least cycle 6 of immunotherapy without experiencing dose limiting toxicity (DLT). While a true feasibility rate of ≥80% (ie, DLT occurring in ≤20%; exclusion of patients with other reasons than DLT for treatment discontinuation) was considered to be clearly acceptable, an actual feasibility in only ≤65% was defined as a negative result. Based on these proportions, and applying a standard one-stage design for pilot studies according to Fleming,²⁰ 57 patients qualifying for RIT treatment were required to assess the feasibility, with a type I error of 0.05 and a power of 80%.

The median follow-up duration was calculated as (un-adjusted) median of the follow-up of all patients. Event-related data were analyzed according to the product limit method of Kaplan and Meier. The explorative comparison of HPV positive oropharyngeal with other tumors was performed with the log rank test. CIs always refer to 95%.

All biomarker analyses were explorative. Univariate logistic regression was used to evaluate the association of the clinical and pathological factors with treatment failure. Multivariate logistic regression was used to evaluate the adjusted association of the absolute immune cell counts or fraction of peripheral blood immune markers with treatment failure (glm.fit function).

Statistical analyses were carried out using the software package R V.3.6.1 (R Foundation for Statistical Computing) and NCSS.

RESULTS

Patient characteristics

Eighty patients were enrolled from September 2018 to May 2020 in eight German centers. Data cut-off was June 7, 2021. One patient did not receive any study treatment due to tumor bleeding and was excluded from all analyses. Baseline characteristics are given in table 1. During the trial the TNM seventh edition was replaced by the eighth edition. Consequently, all tumor stages were adapted to the eighth edition. In addition the UICC stages according to the TNM seventh edition are given in online supplemental table 1. PD-L1 status of tumor and immune cells was scored as percentage of PD-L1 positive area of total tumor or immune cell area, respectively, with the previously established cut-off value of 25% for durvalumab ± tremelimumab in HNSCC.²¹

Treatment parameters and feasibility analysis

Seventy-nine patients received induction chemo-immunotherapy (figure 1). Seven patients (9%) received carboplatin instead of cisplatin. Two patients developed relevant toxicity after induction chemotherapy and consequently received no immune checkpoint inhibitors. Restaging assessment including rebiopsy of the primary tumor was performed in 76 of 79 treated patients. Pathologic response was pCR in 41 patients (52%, 95% CI 37% to 60%). Of the remaining 35 patients, 31 (39%) had an intratumoral increase of CD8 +immune cells, with a median increase by factor 3.0. Taken together, 72 patients fulfilled the criteria to continue trial treatment. Out of these, seven patients had to be excluded due to toxicity, mainly elevated transaminases/hepatitis (n=4), and five patients opted for alternative treatments. Taken together, 19 patients treated with induction chemo-immunotherapy did not enter RIT and mostly received radiotherapy combination treatments in a curative intent (17 patients, detailed information in online supplemental table 2). Thus, 60 patients (76%) entered RIT representing the primary endpoint cohort, which

Table 1 Patient characteristics of treated patients

	No (n=79)	%
Age (median, SD)	60.2±8.6 years	
Sex		
Male	65	(82)
Female	14	(18)
ECOG performance status		
0	62	(78)
1	17	(22)
Primary tumor site		
Oral cavity	10	(13)
Oropharynx	43	(54)
Hypopharynx	14	(18)
Larynx	12	(15)
T category		
T1	5	(6)
T2	12	(15)
T3	17	(22)
T4	45	(57)
N category		
N0	20	(25)
N1	18	(23)
N2	29	(37)
N3	12	(15)
UICC stage (according to TNM eighth edition)		
II*	5	(6)
III	30	(38)
IV	44	(56)
Tobacco smoking status		
Current smoker	33	(42)
Former smoker	33	(42)
Never smoker	13	(16)
Pack years of current/former smokers (median, SD)	40.0±18.3 pack years	
Intratumoral CD8 +immune cells (IC) (median, range)	391 cells/mm ² (12–5984)	
PD-L1 status		
Tumor cells		
<25%	61	(77)
≥25%	18	(23)
IC area		
<25%	49	(62)
≥25%	30	(38)
Algorithm positivity		
Negative	40	(51)
Positive	39	(49)
HPV status all tumors (p16 positivity)		

Continued

Table 1 Continued

	No (n=79)	%
Negative	53	(67)
Positive	26	(33)
HPV status Oropharynx only (p16 positivity) (n=43)		
Negative	20	(47)
Positive	23	(53)

*The TNM version changed from the seventh edition to the eighth edition during the trial. TNM classification in this table is according to the eighth edition. TNM classification according to the seventh edition is given in online supplemental table 1.

HPV, human papilloma virus; PD-L1, programmed death protein ligand 1; TNM, TNM Classification of Malignant Tumors.

fulfills the predefined calculated sample size of n=57 subjects to analyze the primary endpoint feasibility until cycle 6 of immunotherapy. Radiotherapy to a cumulative dose of at least 66.0/59.4/50.8 Gy (at least 33 of planned 35 fractions) was delivered in 59 patients. One patient terminated radiotherapy prematurely without toxicity on her own request (no DLT). Immunotherapy was terminated before cycle six in three additional patients for other reasons than DLT, which were excluded from the feasibility analyses according to the study protocol. Ten patients experienced DLT, namely three cases of elevated transaminases/hepatitis, two cases of arthritis, one nephritis, one pancreatitis, one adrenalitis, one pneumonitis and one hypothyroidism. Forty-six patients received immunotherapy until at least cycle 6. This results in a feasibility rate of 82% (46/56), meeting the primary endpoint of the study, as the lower boundary of the one-sided 95% CI is 72%, thus excluding the pre-defined level of unacceptable feasibility ($\leq 65\%$). In addition to this protocol-specified feasibility analysis, an additional analysis of the entire treatment scheme was performed. In the entire treatment scheme consisting of induction chemo-immunotherapy and RIT 46 of 79 patients (58%) completed cycle six of immunotherapy, whereas after exclusion of ten non-toxicity-related drop outs the overall feasibility rate was 67% (46/69).

Survival analyses

Key secondary endpoints were PFS and OS. The median follow-up was 17.2 months. All patients on treatment completed the protocol-defined restaging assessment 12 weeks after RIT, which was mainly performed with 18F-FDG PET/CT. In the RIT cohort (primary endpoint cohort, n=60) 17 PFS events (28%) and ten deaths (17%) were observed. In the entire study cohort 25 PFS events (32%) and 16 deaths (20%) were detected. Locoregional progression, distant metastases or both appeared in eight, two and one patients in the RIT cohort and nine, four and two patients in the entire cohort, respectively. Three patients receiving neck dissection ≤ 20 weeks after completion of radiotherapy with pathological detection of residual tumor were not classified as PFS events.

In the RIT cohort the 1-year and 2-year PFS rate was 78% and 72%, respectively (figure 2A), and the 1-year and 2-year OS rate was 90% and 84%, respectively (figure 2B). Patients who did not continue with RIT after induction treatment had a 1-year and 2-year PFS rate of 63% and 58% and a 1-year and 2-year OS rate of 79% and 67% (online supplemental figure 1). In the entire cohort the 1-year and 2-year PFS rate was 75% and 68%, respectively (figure 2C), and the 1-year and 2-year OS rate was 87% and 79%, respectively (figure 2D).

An explorative subgroup analysis of HPV-associated p16 positive oropharyngeal cancers (n=23) detected one case of distant metastases in the RIT cohort and one death in the patients with alternative treatment. There was no locoregional failure in this subgroup. The 2-year PFS rate was 94% in the RIT cohort and 91% in the entire cohort (online supplemental figure 2). Patients with other than p16 positive oropharyngeal tumors achieved a 2-year PFS rate of 64% in the RIT cohort and 59% in the entire cohort. In both cohorts, PFS and OS were significantly longer in p16 positive oropharyngeal tumors.

Safety analyses

Adverse events (AEs) of any cause (treatment related or unrelated) occurring in at least 5% of treated patients are listed in table 2. In addition, AE possibly related to immunotherapy (immune-related AEs, irAE) occurring in any patient are listed. Among all patients treated, 73 patients (92%) experienced a grade 3 AE and 14 patients (18%) experienced a grade 4 AE, with 74 patients (94%) having at least one grade 3–4 AE. There appeared no grade 5 AE.

Most common grade 3–4 AE were typical chemotherapy-related events as leukopenia (52%) and infections (32%). Further very common AE grade 3–4 were typical radiotherapy-related, such as dysphagia (53%), stomatitis (14%) and radiation dermatitis (9%).

AE grade 3–4 possibly related to immunotherapy occurred in 23 patients (29%) and mainly included elevated transaminases/hepatitis in eight patients (10%) and diarrhea/colitis in five patients (6%). Out of these, two patients recovered from elevated transaminases/hepatitis without additional treatment (one had no prior immune checkpoint inhibitor treatment). The other six patients with elevated transaminases/hepatitis received glucocorticoids, one in combination with mycophenolat-mofetil. All patients recovered, whereas one developed a primary sclerosing cholangitis as possible late complication. Endocrinopathies of any grade included hyperthyroidism (18%) that resulted in subsequent hypothyroidism (19%) in most cases. Endocrinopathies grade 3 included adrenalitis and hypophysitis with two cases each that were treated with hydrocortisone replacement.

Two patients developed COVID-19 disease during study treatment. Both patients had only mild symptoms, but one patient was withdrawn from the study due to delayed restaging assessments.

Figure 1 CONSORT diagram. *Radiotherapy to a cumulative dose of at least 66.0/59.4/50.8 Gy. CD8, CD8 +intratumoral immune cells. CONSORT, Consolidated Standards of Reporting Trials; DLT, dose-limiting toxicity; IT, immunotherapy; pCR, pathologic complete response; RIT, radioimmunotherapy; RT, radiotherapy.

Biomarker analyses

Treatment failure defined as locoregional tumor recurrence, residual locoregional disease or distant metastases (RRM) served as endpoint for the explorative biomarker analysis in the RIT cohort. A total of 55 patients treated with RIT provided full availability of pathological and liquid immune parameters (out of 60 patients, 92%) and were included in this analysis. Intratumoral CD8 +immune cell density and PD-L1 on tumor cells were not associated with treatment failure (figure 3A,B). Low PD-L1 immune cell area predicted treatment failure (RRM; $p=0.0419$, figure 3C). In the analysis of liquid immune parameters,

all analyzed 54 immune cell subsets were normalized for these three parameters and additionally for T-stage and HPV/p16 status. The rare immune cell subsets human leukocyte antigen – DR isotype (HLA-DR) expressing B cells, dendritic cells (DC) and their subgroup myeloid DCs (mDC) and double negative T cells (DNT) were significantly associated and further 11 immune cell subsets mainly from the innate compartment tended to be associated ($p<0.2$) with RRM (figure 3D–G, online supplemental table 3). The slight, but significant differences of immune cell subsets in the peripheral blood when comparing RRM with non-RRM are in the expected

Figure 2 Kaplan-Meier estimates of progression-free (PFS) and overall survival (OS). Kaplan-Meier estimates of (A) PFS and (B) OS of the radioimmunotherapy (RIT) cohort. Kaplan-Meier estimates of (C) PFS and (D) OS of the entire study cohort. Tick marks indicate censored observations.

range for serving as immune biomarkers in cancer disease.²²

DISCUSSION

In the CheckRad-CD8 trial, patients were treated with induction chemo-immunotherapy followed by RIT with combined PD-L1/CTLA-4 inhibition after intratumoral CD8 +immune cell-based selection. The primary endpoint was the feasibility of RIT with concomitant durvalumab and tremelimumab followed by maintenance therapy. Durvalumab and tremelimumab were administered concomitantly for four cycles, followed by eight cycles of durvalumab maintenance. This schedule was chosen similar to the treatment of melanoma with nivolumab/ipilimumab²³ and based on previous combination studies of durvalumab/tremelimumab, which

defined it as standard regimen that was also used in the phase III EAGLE and KESTREL trials.²¹ The feasibility of durvalumab and tremelimumab in combination with platinum-doublet chemotherapy was first demonstrated in the Canadian IND226 trial in different tumor entities.²⁴ Preliminary data from the induction phase of the CheckRad-CD8 also reported the combination of durvalumab/tremelimumab with cisplatin/docetaxel before.¹⁶

Patient selection for RIT was based on pathological assessment of the re-biopsy. A high rate of 52% of the patients developed a biopsy-proven pCR after single cycle induction chemoimmunotherapy, which is comparable to subgroup analyses of two trials with biopsy-proven pCR rates between 42% and 64% after three cycles TPF.^{25,26} A phase II trial with three cycles of TPF induction prior to planned surgery achieved a pCR of 33% at the primary

Table 2 Adverse events (AE) of treated patients

n=79 patients	Grade 1–2		Grade 3		Grade 4	
	No	%	No	%	No	%
Non immune-relate AE appearing in ≥5% of patients (non-irAE)						
Alopecia	64	(81)	0		0	
Fatigue	52	(66)	8	(10)	0	
Xerostomia	55	(70)	4	(5)	0	
Dysphagia	15	(19)	42	(53)	0	
Infection	29	(37)	23	(29)	2	(3)
Leukopenia	13	(16)	31	(39)	10	(13)
Stomatitis	40	(51)	11	(14)	0	
Radiation dermatitis	42	(53)	7	(9)	0	
Nausea	41	(52)	3	(4)	0	
Pain	38	(48)	5	(6)	0	
Pruritus	37	(47)	0		0	
Constipation	32	(41)	0		0	
Vertigo	30	(38)	1	(1)	0	
Lymph edema	30	(38)	0		0	
Vomiting	25	(32)	1	(1)	0	
Oral thrush	25	(32)	0		0	
Polyneuropathy	23	(29)	0		0	
Thrombocytopenia	20	(25)	0		0	
Hypokalemia	13	(16)	3	(4)	0	
Dyspnea	15	(19)	0		0	
PEG/catheter complication	10	(13)	5	(6)	0	
Hoarseness	14	(18)	0		0	
Renal insufficiency	10	(13)	3	(4)	1	(1)
Subcutaneous fibrosis	13	(16)	0		0	
Hyperpigmentation	12	(15)	0		0	
Anemia	8	(10)	3	(4)	0	
Hearing disorder	11	(14)	0		0	
Ear disorder	9	(11)	1	(1)	0	
Hyponatremia	4	(5)	4	(5)	0	
Bleeding	5	(6)	1	(1)	1	(1)
Edema	6	(8)	1	(1)	0	
Dysgenusia	4	(5)	1	(1)	0	
Weight loss	3	(4)	2	(3)	0	
Ulcer (tumor location)	3	(4)	0		1	(1)
Trism	4	(5)	0		0	
Any possibly irAE						
Diarrhea/colitis	40	(51)	5	(6)	0	
Skin reaction	27	(34)	0		0	
Elevated transaminases/ hepatitis	7	(9)	6	(8)	2	(3)
Hypothyroidism	14	(18)	1	(1)	0	
Hyperthyroidism	14	(18)	0		0	
Arthritis	4	(5)	1	(1)	0	
Increased lipase/pancreatitis	0		3	(4)	0	

Continued

Table 2 Continued

n=79 patients	Grade 1–2		Grade 3		Grade 4	
	No	%	No	%	No	%
Adrenalitis	0		2	(3)	0	
Hypophysitis	0		2	(3)	0	
Nephritis	1	(1)	1	(1)	0	
Pneumonitis	0		0		1	(1)

Non-irAE appearing in at least 5% of patients independent from relationship to treatment and all possibly irAE.
PEG, percutaneous endoscopic gastrostomy.

tumor in the surgical specimen.²⁷ This indicates a limitation that in the biopsies the pCR rate may be estimated too high, as viable tumor at other areas may have been missed. In order to ensure the correct location of the biopsies in case of pCR, the pathological assessment in the CheckRad-CD8 trial included the identification of a former tumor bed by the detection of a relevant resorptive inflammation in conjunction with granulation and scar tissue.

Four phase I–II trials using PD-1/PD-L1 inhibitors alone or in combination with CTLA-4 inhibitors reported only three cases with pCR derived from complete surgical specimen out of 89 enrolled patients.^{28–31} In contrast, the CheckRad-CD8 trial investigated tumor biopsies as tumors were not submitted to surgical resection. However, the markedly high rate of pCR indicates the high efficacy of the applied combined chemoimmunotherapy, though there may be some degree of false positive pCR in this cohort. In a recent retrospective analysis, the single cycle induction chemoimmunotherapy of the CheckRad-CD8 trial was more efficient than single cycle induction chemotherapy alone.³² The combination with immunotherapy may allow a reduction of the number of treatment cycles of induction chemotherapy in future, which can increase the rate of patients entering curative radio(chemo)therapy. This is probably an advantage as for example, in the TAX 324 trial 21%–25% of the patients did not receive radiochemotherapy after induction treatment.³³ In comparison, in the CheckRad-CD8 trial 60 patients (76%) received RIT in the trial and 17 patients (22%) other radiotherapy combinations outside the study. Only one patient received chemotherapy alone and one refused further treatment (together 3% without radiotherapy).

Besides the patients with pCR further 39% of the patients of the CheckRad-CD8 trial intratumoral CD8 +cells increased. Increasing CD8 +immune cells have previously been reported as predictor for treatment response to PD-1 inhibitors in sequential biopsies of melanoma patients.³⁴

The primary endpoint of the CheckRad-CD8 trial was feasibility of RIT with combined durvalumab and tremelimumab with subsequent maintenance therapy until cycle 6. This endpoint was chosen as it is the time point of the re-staging assessment 12 weeks after completion of RIT³⁵

and only patients with no residual tumor continue further maintenance immunotherapy. The feasibility rate of the RIT with maintenance treatment until cycle six of 82% met the predefined cut-off for the primary endpoint. The overall feasibility rate of the entire treatment including induction chemo-immunotherapy and RIT with maintenance treatment until cycle six was 67%. This result is comparable to the TAX 324 trial with three cycles of TPF or PF before radiochemotherapy that achieved the completion of radiochemotherapy in 68%–73% of the patients.³³ This is an important finding considering that previous feasibility data of radiotherapy and immune checkpoint inhibitors mostly include only a single drug. Only three small phase I–II trials combined durvalumab/tremelimumab combination and stereotactic radiotherapy in different metastatic tumors so far and reported no safety problems.^{36–38} Similarly, no severe radiotherapy-related toxicity as soft-tissue necrosis or ulcers was detected in the CheckRad-CD8 trial. The frequency of typical radiotherapy-related head and neck treatment toxicity as dysphagia, stomatitis or dermatitis was lower than in the previous trial in this indication (PacCis-RCT) of the same study group.³⁹

However, elevated transaminases/hepatitis grade 3oc–4ocurred in 10% (n=8). Two cases were probably induced by docetaxel and recovered without further treatment and six cases received immunosuppressive treatment due to suspected autoimmune hepatitis. Accordingly, the experienced rate of grade 3–4 increased transaminases/hepatitis is increased compared with 1% for durvalumab/tremelimumab combination in the EAGLE study²¹ and to 3% for additional chemotherapy in the IND226 study.²⁴ The second most common irAE grade 3–4 was diarrhea with 6% compared with 9% in the IND226 study and 1% without chemotherapy in the EAGLE study. Any grade 3–4 irAE appeared in 29% of patients in CheckRad-CD8, which is comparable to 21% in the IND226 study.

A phase Ib trial previously reported the feasibility of the combination of radiochemotherapy with weekly cisplatin and concomitant pembrolizumab.⁴⁰ Two randomized phase III trials combined radiochemotherapy with high-dose cisplatin and pembrolizumab or avelumab, respectively.^{3,4} Whereas the Keynote-412 trial is still ongoing, the Javelin Head and Neck 100 trial was negative regarding its primary endpoint PFS,⁵ which highlights the need for

Figure 3 Predictive immune parameters of treatment failure. Comparison of the histological parameters (A) intratumoral CD8 +cell density as determined by immunohistochemistry, (B) programmed cell death ligand 1 (PD-L1) tumor cell area (TC area), (C) PD-L1 immune cell area (IC area) and the liquid immune parameters (D) dendritic cells (DC; LIN-/HLA-DR+), (E) myeloid DCs (mDC; LIN-/HLA-DR+/CD11c high, CD1c-, CD123 low), (F) double negative T cells (DNT; CD3+/CD4-/CD8-), and (G) HLA-DR +B cells (CD19+/CD20+) in patients with locoregional tumor recurrence, residual locoregional disease or distant metastases (RRM) and without RRM (non-RRM). HLA-DR, human leukocyte antigen – DR isotype.

new, possibly chemotherapy-free, treatment schemes. The CheckRad-CD8 trial achieved a PFS rate of 78% and 72% after one and 2 years in the RIT cohort and 75% and 68% in the entire cohort compared with approximately 70% and 58% in the Javelin Head and Neck 100 trial (data from trending superior control arm).⁵ OS was comparable in both trials. In both trials approximately one third of all tumors were p16 positive. This highlights the promising efficacy of chemotherapy-free radiotherapy with double immune checkpoint blockade. The decrease of PFS at 5–6 month after study inclusion represents the high sensitivity of a mostly 18F-FDG PET/CT based restaging to

detect residual tumor.^{35 41} The efficacy is supported by a study comprising 29 cisplatin-ineligible patients treated with radiotherapy and pembrolizumab followed by three cycles of pembrolizumab as maintenance therapy that achieved a 2-year PFS rate of 71%.⁴² However, maintenance therapy seems to be essential, as the phase II PembroRad study only had a 2-year PFS rate of 42% with radiotherapy and concomitant pembrolizumab without subsequent maintenance therapy.⁴³ In the CheckRad-CD8 trial no locoregional failure appeared in HPV-associated oropharyngeal cancer (n=23). In general, the strong immune cell infiltration of these tumors, especially

with PD-1 positive immune cells, makes them a promising subgroup for immunotherapy.¹² In a previous analysis of the CheckRad-CD8 trial HPV positive tumors had a significantly higher intratumoral CD8 +immune cell density and a higher intratumoral PD-L1 immune cell area.¹⁶ Whereas single clinical trials found a better outcome of HPV positive tumors during immune checkpoint inhibition, a recent meta-analysis was negative.^{44,45} In the CheckRad-CD8 trial these patients had an excellent prognosis with a 2-year PFS rate of 94% in the RIT cohort. However, it has to be considered that these patients also have a very good prognosis on platinum-based radiochemotherapy as demonstrated in the RTOG 1016 trial.⁴⁶ Thus, these patients may not benefit from additional treatment with immune checkpoint inhibitors due to additional side effects. On the other hand, immunotherapy may give the opportunity for future radiotherapy dose de-escalation trials.

Compared with the treatment scheme of the TAX324 trial consisting of classical TPF induction chemotherapy (vs PF induction) followed by radiochemotherapy, the CheckRad-CD8 trial achieved good results. The 2-year PFS rate of TAX 324 was 53% in the superior TPF arm compared with 68% in the entire cohort of CheckRad-CD8.³³ In both trials the results in HPV positive oropharyngeal cancers (2-year PFS of entire study cohorts: CheckRad-CD8 91% and TAX 324 83%) were superior to HPV negative oropharyngeal cancers and other locations (2-year PFS of entire study cohorts: CheckRad-CD8 59% and TAX 324 35% (HPV negative oropharyngeal cancer only)).⁴⁷

In the light of the negative phase III EAGLE²¹ and KESTREL trials⁴⁸ investigating durvalumab/tremelimumab combination in the recurrent/metastatic setting, the role of tremelimumab as combination partner for durvalumab has to be re-evaluated. As tremelimumab enhances T-cell priming in an early phase of the immune reaction, the combination with a single PD-(L)1 inhibitor that only can release a pre-existing immune reaction is probably not efficient. Nevertheless, the combination with cell death inducing agents as chemotherapy (especially taxanes⁴⁹ or radiotherapy, which was the strategy of the CheckRad-CD8 study, may release a benefit of tremelimumab therapy.^{50,51}

In explorative analyses of the Javelin Head and Neck 100 trial the only subgroup with benefit from the PD-L1 blockade were patients with ≥25% PD-L1 tumor staining, which highlights the need for patient selection.⁵ In the CheckRad-CD8 trial PD-L1 on immune cells, but not on tumor cells tended to predict treatment failure, which was also reported for PD-1 inhibitor monotherapy.⁵² A new finding of the CheckRad-CD8 study is the predictive role of liquid immune parameters for RIT, especially cell subsets derived from the innate immune system, which was also described for immune checkpoint inhibitor monotherapy.^{53,54} The rare immune cell populations DCs and their subgroup mDCs and DNT cells were significantly enhanced in the peripheral blood of patients with

treatment failure. HLA-DR expressing B cells were significantly reduced. These cell types might be the trigger of immune suppression in these patients.^{55,56} Thus, the knowledge about peripheral immune subsets is probably essential for understanding the mechanisms involved in RIT combinations.

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