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Original Research Article

RADIANCE – Radiochemotherapy with or without Durvalumab in the treatment of anal squamous cell carcinoma: A randomized multicenter phase II trial

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ABSTRACT

Purpose: Anal squamous cell carcinomas (ASCC) are increasing in frequency across the developed world. The 3-year disease-free survival (DFS) in patients with locally-advanced disease is approximately 60% after primary radiochemotherapy (RCT). There is a strong rationale for combining immunotherapy with RCT in patients with ASCC due to its association with human papilloma virus (HPV) infection.
Methods/design: RADIANCE is an investigator initiated, prospective, multicenter, randomized phase II trial testing the addition of Durvalumab, a PD-L1 immune checkpoint inhibitor, to standard RCT in 178 patients with locally advanced ASCC (T2 $\geq$ 4 cm Nany, cT3-4 and/or cN+). In the control arm, patients will be treated with standard mitomycin C (MMC)/5-fluorouracil (5-FU)-based RCT. Intensity-modulated radiotherapy (IMRT) will be applied as follows: PTV_A (primary tumor) T1-T2 < 4 cm N+: 28 $\times$ 1.9 Gy =

Abbreviations: ASCC, anal squamous cell carcinoma; cCR, clinical complete response; RCT, radiochemotherapy; DFS, disease-free survival; MMC, mitomycin C; OS, overall survival; PD-1, programmed death receptor 1; PD-L1, programmed death receptor ligand 1; RT, radiotherapy; 5-FU, 5-fluorouracil; MRI, magnetic resonance imaging; CT, computed tomography.

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Radiochemotherapy
Phase 2
Disease-free survival

53.2 Gy; *or* T2 ≥ 4 cm, T3-4 Nany: 31 × 1.9 Gy = 58.9 Gy; PTV_N (involved node): 28 × 1.8 Gy = 50.4 Gy ; and PTV_Elec (elective node): 28 × 1.43 Gy = 40.0 Gy over a period of 5,5–6 weeks. Concomitant chemotherapy will be administered using MMC with 5-FU during weeks 1 and 5 of radiotherapy (MMC 12 mg/m^2, day 1 [maximum single dose 20 mg]; 5-FU 1000 mg/m^2 days 1–4 and 29–32). In the experimental arm, Durvalmab (1500 mg absolute dose, intravenously) will be combined with the same RCT as in the control arm. Immunotherapy with Durvalumab will start 14 days before initiation of standard RCT, administered every four weeks (q4w) thereafter for a total of twelve doses. The primary endpoint is disease-free survival (DFS) after 3 years.

Discussion: As ASCC is considered an immunogenically "hot" tumor due to its association with HPV infection, the combination of RCT with Durvalumab may improve tumor control and long-term clinical outcome in this patient collective compared to RCT alone.

1. Background

Anal squamous cell carcinomas (ASCC) are increasing in frequency across the developed world. There is a strong rationale for combining the PD-L1 immune checkpoint inhibitor Durvalumab with radiochemotherapy (RCT) in patients with ASCC. First, although primary RCT with concurrent mitomycin C and 5-fluorouracil (MMC/5-FU) is the standard treatment for ASCC, the 3-year disease-free survival (DFS) in patients with locally-advanced disease is approximately 60% [1–4]. Notably, despite several randomized trials aiming at treatment optimization, the standard therapy has not changed over the past 30 years. Second, approximately 80–90% of patients with ASCC are human papilloma virus (HPV)-positive, which is associated with higher tumor "immunogenicity" in this malignancy that is known to correlate with better response to RCT as well as PD-1/PD-L1 immune checkpoint inhibitors [5,6]. Also, PD-L1 expression was observed in 33%-62% of patients with locally advanced non-metastatic ASCC that correlated with tumor stage [5,7]. Third, inhibition of the PD-1/PD-L1 axis showed encouraging responses in recurrent/metastatic ASCC in two phase Ib/II trials [8,9]. Fourth, several data indicate complementary roles between R(C)T and immunotherapy: R(C)T can, via immunogenic cell death, lead to upregulation of major histocompatibility class I (MHC I) molecules, induction of the CD95 Fas receptor, release of various cytokines and danger signals (ATP, calreticulin, High-Mobility-Group-Protein B1), activation of prophagocytic signals and increased antigen presentation with subsequent enhanced antigen presentation, recruitment of dendritic cells and activation of cytotoxic CD8+ T-cells [10], whereas immune checkpoint inhibition can reinvigorate T-cells by enhancing their cytotoxic function and motility [11,12]. Accordingly, numerous preclinical studies have demonstrated enhanced radiosensitization using immune checkpoint inhibitors in melanoma, breast, pancreatic, colorectal cancer and glioblastoma multiforme [13–17]. Fifth, R(C)T can induce PD-L1 upregulation with resulting dysfunction in CD8+ T-cells, and addition of anti-PD-L1 to RCT can overcome T-cell suppression to reinvigorate immune surveillance [18]. Thus, based on the above data, RCT combined with Durvalumab is expected to be more effective than primary RCT alone. In a large randomized phase III trial in patients with locally-advanced non-small cell lung cancer, the addition of Durvalumab to RCT led to significant improvement of approximately 20% in progression free survival (PACIFIC trial) [19]. Altogether, the RADIANCE multicenter, randomized phase II trial aims to improve the current standard treatment by incorporating Durvalumab to the primary MMC/5-FU-based RCT in patients with locally-advanced ASCC.

2. Methods/design

2.1. Study setting

The RADIANCE trial is a prospective, multicenter, randomized phase II trial. Only patients with histologically-confirmed, locally-advanced (T2 ≥ 4 cm Nany: stage IIA, stage IIB-IIIC: cT3-4 and/or cN+, according to the American Joint Committee on Cancer TNM Staging Classification, 8th ed., 2017) ASCC will be screened for this trial. Of note, previous studies [20–22] have demonstrated worse survival rates in patients with tumors ≥4 cm, which consisted the rationale for including patients T2 ≥ 4 cm Nany in the RADIANCE trial. After signing informed consent, all patients will be prospectively randomized to either control or experimental arm in a 1:1 ratio. Altogether 22 centers throughout Germany (21) and Switzerland (1) will participate in this trial with an anticipated minimum recruitment of 3–5 patients per year and a maximum of 15 patients per year and center. The study overview with the treatment schedule in both arms is shown in Fig. 1. The inclusion and exclusion criteria are summarized in Table 1.

2.2. Clinical endpoints

DFS is the primary endpoint of the study**.** DFS is defined as the time between randomization and the first of the following events: (a) non-complete clinical response at restaging magnetic resonance imaging (MRI) and proctoscopy, including biopsies of suspicious findings, 26 weeks after initiation of RCT, (b) loco-regional recurrence after initial complete clinical response (cCR), (c) distant metastases, (d) second primary cancer, or (e) death from any cause, whichever occurs first. Patients without any of these events are censored at the time point of last observation. The primary aim is to improve DFS by adding the PD-L1 immune checkpoint inhibitor Durvalumab to standard MMC/5-FU-based RCT in patients with locally-advanced (T2 ≥ 4 cm Nany, stage IIB-IIIC: cT3-4 and/or cN+) ASCC. Our hypothesis is that addition of Durvalumab to primary RCT will increase the 3-year DFS rate from 60% (control arm) to 80% (experimental arm).

Secondary endpoints are acute toxicities, rate of complete remissions 26 weeks after initiation of RCT, overall survival (OS), colostomy free-survival (CFS), cumulative incidence of local and distant recurrences, Quality of Life according to EORTC QLQ–C30 (version 3.0) and functional outcome per EORTC QLQ-ANL27, and various translational and biomarker studies as part of a translational research program including analyses of primary tumor and blood samples.

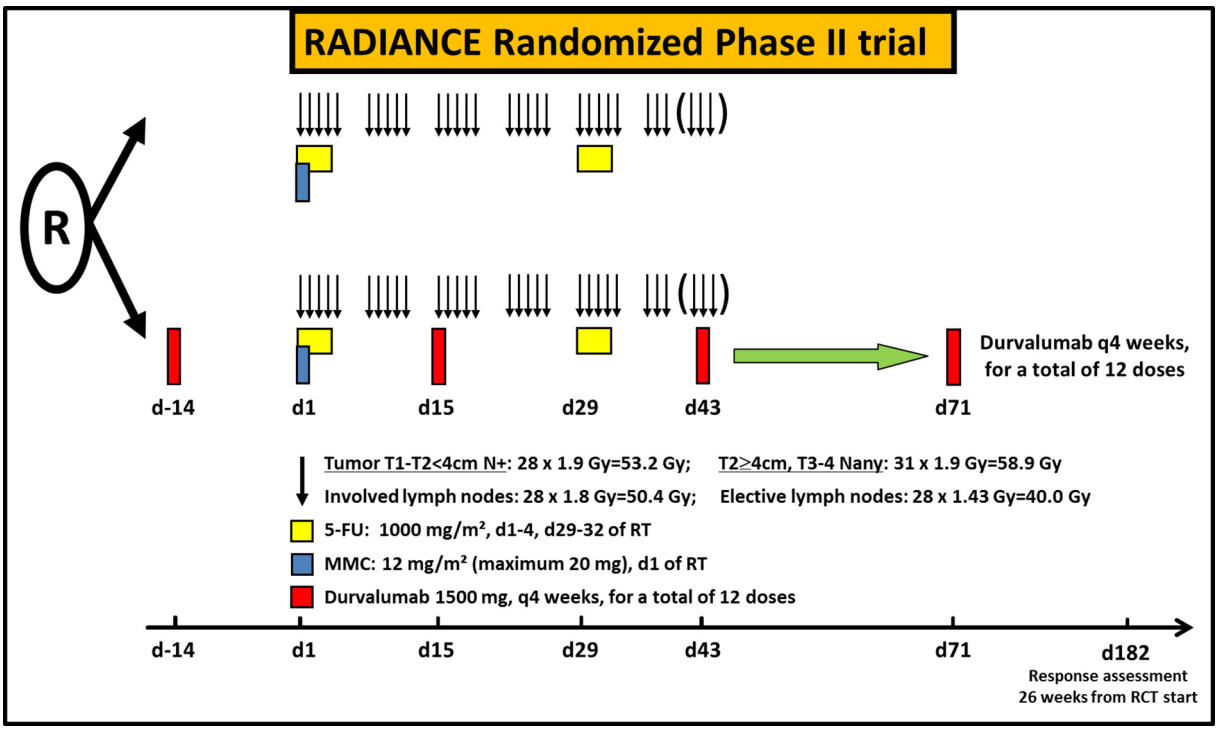

Fig. 1. Overview of the RADIANCE trial. In the control arm (upper row), patients with ASCC will be treated with standard primary 5-FU/MMC RCT, as indicated. In the experimental arm (lower row), 5-FU/MMC RCT will be combined with the PD-L1 immune checkpoint inhibitor Durvalumab. Of note, Durvalumab will be initiated 14 days prior to RCT start, and will be administered every 4 weeks thereafter (q4w) for a total of 12 doses. The x-axis indicates the time in days. Abbreviations: R, randomization; ASCC, anal squamous cell carcinoma; 5-FU, 5, fluorouracil; MMC, mitomycin C; RCT, radiochemotherapy;

2.3. Treatment schedule

The prescribed radiotherapy doses are based on the UK guidelines for IMRT in anal canal for primary tumors T1-T2 < 4 cm, and involved lymph nodes as well as elective lymph nodes [23]. However, for large tumors i.e. T2 $\geq$ 4 cm and T3-4, a fractionation regimen with higher total radiotherapy dose of approximately 60 Gy is used considering the NCCN/RTOG guidelines, and previous and recent literature indicating better local control for higher doses close to 60 Gy in those large tumors [21,24]. Chemotherapy prescription is according to the ESMO guidelines [25] that is also similar to the NCCN guidelines [26].

In the control arm, patients will be treated with standard MMC/5-FU-based RCT. Intensity-modulated radiotherapy (IMRT) will be applied as follows: PTV_A (primary tumor) T1-T2 < 4 cm N+: 28 $\times$ 1.9 Gy = 53.2 Gy; *or* T2 $\geq$ 4 cm, T3-4 Nany: 31 $\times$ 1.9 Gy = 58.9 Gy; PTV_N (involved node): 28 $\times$ 1.8 Gy = 50.4 Gy ; and PTV_Elec (elective node): 28 $\times$ 1.43 Gy = 40.0 Gy over a period of 5,5–6 weeks. Concomitant chemotherapy will be administered using MMC with 5-FU during weeks 1 and 5 of radiotherapy (MMC 12 mg/m^2, day 1 [maximum single dose 20 mg]; 5-FU 1000 mg/m^2 days 1–4 and 29–32).

Patients randomized in the experimental arm will receive the same RCT as in the control arm but with the first Durvalumab application within 14 days after randomization. Immunotherapy with Durvalumab (1500 mg absolute dose, intravenously) will start 14 days before initiation of RCT and will be given every four weeks (q4w) thereafter for a total of twelve doses i.e. to a total duration of 1 year. The rationale for administering Durvalumab 14 days before initiation of RCT in the experimental arm is preclinical evidence showing that immune checkpoint inhibition can reinvigorate the immune system and enhance response to RCT. This delay is not clinically relevant. Patients will receive Durvalumab unless there is unacceptable toxicity, withdrawal of consent or another discontinuation criterion is met (e.g., an individual patient will not receive any further Durvalumab if their weight falls to 30 kg or less). The first fraction of radiotherapy has to be applied within 14 days for the control arm and 21 days for the experimental arm (±3 days) after randomization.

2.4. Pilot phase

A first safety analysis will be performed after the inclusion of 10 patients in the experimental arm. The toxicity evaluation period for the pilot phase starts from the onset of treatment and continues up to 16 weeks upon initiation of treatment with Durvalumab (time of first follow-up examination after RCT). If one of the first 10 patients develops predefined toxicity levels up to 16 weeks from initiation of Durvalumab treatment, an additional 10 patients will be treated. Predefined toxicity is summarized in Table 2. The trial will be held if predefined toxicity levels occur in $\geq$ 2 of 20 patients up to 16 weeks from initiation of Durvalumab, and discussed with the Data Safety Monitoring Board for possible amendments.

2.5. Follow-up

The follow-up will include clinical and radiological assessment of tumor status as well as clinical and laboratory examination. Tumor response and staging will be assessed using digital rectal examination (DRE) and proctoscopy, inguinal node palpation, pelvic MRI, abdomen sonography and chest X-ray/(computed tomography (CT)). The follow-up schedule for both arms is summarized in Table 3. If a DFS event occurs, treatment within the clinical trial will be stopped. In that case, treatment of local and/or distant recurrence will be performed according to the in-house and international guidelines following discussion at the multidisciplinary tumor board.

Table 1
Main inclusion and exclusion criteria of the RADIANCE trial.

Inclusion criteria	• Histologically-confirmed ASCC of the anal canal or the anal margin • UICC-Stage IIB-IIIC including T2 ≥ 4 cm Nany (IIB: T3N0M0; IIIA: T1-2N1M0; IIIB: T4N0M0; IIIC: T3-4N1M0; T2 ≥ 4 cm Nany) according to proctoscopy, pelvic MRI, CT scan of thorax and abdomen, all within 30 days prior to recruitment • ECOG-Performance score 0–1 • Life expectancy of >12 months • Body weight >30 kg • Adequate function of bone marrow, liver and kidney as defined by laboratory tests • Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up. • For HIV-positive patients: running combined antiretroviral therapy (CART) on a stable dose at study entry and undetectable HIV-viral load (HIV Viral load <50 copies/mL and CD4 > 200/μL). Patients will be closely monitored and CART management will be performed according to appropriate labelling guidance of the antiviral therapy. CART should be on a stable dose at study entry.
Exclusion criteria	• History of another primary malignancy except for - Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of durvalumab and of low potential risk for recurrence - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease - Adequately treated carcinoma in situ without evidence of disease • Known DPD-deficiency • Any previous treatment with other immunotherapy, a PD1 or PD-L1 inhibitor • Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/d of prednisone, or an equivalent corticosteroid. In case of recent introduction of CART, inclusion will be possible provided subjects had at least 4 weeks of treatment prior to inclusion. • Previous radiotherapy treatment to the pelvis or radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of study drug • History of allogenic organ transplantation. • Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). The following are exceptions to this criterion: - Patients with vitiligo or alopecia - Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement - Any chronic skin condition that does not require systemic therapy - Patients without active disease in the last 5 years may be included but only after consultation with the study chairman - Patients with celiac disease controlled by diet alone • Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent • History of leptomeningeal carcinomatosis or any other metastatic disease • History of active primary immunodeficiency • Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), hepatitis B (known positive HBV surface antigen (HBsAg) result), hepatitis C. Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA. • Receipt of live attenuated vaccine within 30 days prior to the first dose of durvalumab. Note: Patients, if enrolled, should not receive live vaccine whilst receiving durvalumab and up to 30 days after the last dose of durvalumab.

Table 2
Predefined toxicity criteria for the pilot Phase I part of the RADIANCE trial.

Toxicity criteria	• Any Grade 4 immune-mediated adverse event (imAE) • Any ≥Grade 3 colitis • Any Grade 3 or 4 febrile neutropenia • Any Grade 3 or infusion-related reaction (first occurrence and in the absence of steroid prophylaxis) that resolves within 6 h with appropriate clinical management. • Any Grade 3 or 4 non-infectious pneumonitis irrespective of duration • Any Grade 2 pneumonitis that does not resolve to ≤Grade 1 within 3 days of the initiation of maximal supportive care • Any Grade 3 imAE, excluding colitis or pneumonitis, that does not downgrade to Grade 2 within 3 days after onset of the event despite optimal medical management including systemic corticosteroids or does not downgrade to ≤Grade 1 or baseline within 14 days • Liver transaminase elevation >8 × ULN or total bilirubin >5 × ULN • Nephritis: Grade 3 with creatinine >3 × baseline or >3–6 × ULN; Grade 4 with >6 × ULN • Any ≥Grade 3 non-imAE, including allergic reactions, diarrhoea, haematological toxicities and cardiac events such as arrhythmia, except for the exclusions listed below

2.6. Sample size and statistical considerations

The sample size is driven by the primary efficacy outcome (DFS). The 3-year DFS after RCT for locally-advanced ASCC is approximately 60% [2]. In the PACIFIC randomized phase III trial examining the possible benefit of RCT combination with Durvalumab compared with RCT plus placebo in patients with NSCLC, a highly significant improvement in the PFS rate of approximately 20% after 12 months and 18 months was reported [19]. Therefore, we hypothesize that the 3-year DFS rate will show an improvement from 60% in the control arm to 80% in the experimental arm, which would clearly be considered as clinically relevant. In order to detect a difference of this magnitude with a power of 80%, a sample size of 178 patients (89 in each arm using a 1:1 randomization; a drop-out rate of 10% included) is required to reject the null hypothesis of no improvement on a one-sided type I error level of 2.5%. This calculation is based on the application of a log-rank test, on an assumed exponential shape of the survival curves and the drop-out process, as well as a minimum follow-up period of three years for all patients.

Table 3
Follow-up schedule in both arms of the RADIANCE trial.

Evaluation	Time Since Completion of Radiochemotherapy											
	weeks		Months (±1 week)									
	6–8 w	20 w	9	11*	12	15	18	21	24	27	30	36
Physical examination[a]	X	X	X	X	X							
Urine hCG or serum βhCG[b]				X								
Vital signs (temperature, respiratory rate, blood pressure, pulse)				X								
Weight	X		X	X	X							
AE/SAE assessment	X	X	X	X	X	X	X	X	X		X	X
ECOG performance status	X		X	X	X		X		X		X	X
Hematology	X			X		X			X			
Serum chemistry	X			X		X						
Thyroid function tests[c]	X			X								
DRE, inguinal node palpation	X	X	X		X	X	X	X	X		X	X
Proctoscopy	X	X			X		X		X		X	X
Pelvic MRI		X			X		X		X		X	X
Abdomen and thorax CT (or abdomen sonography and thorax X-ray)					X				X			X
EORTC QLQ-C30 and QLQ-ANL27	X				X				X			X
Survival status:						phone contact every 6 months with patients who refuse to return for evaluations and agree to be contacted						

Abbreviations: HCG, human chorionic gonadotropin; AE/SAE, adverse events/ serious adverse events; DRE, digital rectal examination; MRI, magnetic resonance imaging; CT, computer tomography.

* 11 months applies only to the experimental arm and should be performed 30 days after the last dose of durvalumab. It has to be recalculated, if durvalumab has been discontinued earlier.

[a] Full physical exam.

[b] Pre-menopausal female patients of childbearing potential only.

[c] Free T3 and free T4 will only be measured if TSH is abnormal. They should also be measured if there is clinical suspicion of an adverse event related to the endocrine system.

3. Discussion

The main hypothesis of the RADIANCE trial is that incorporation of Durvalumab into standard RCT for patients with locally-advanced ASCC will improve the 3-year DFS in a way that the DFS rate after 3 years is increased to 80% compared to an expected rate of 60% on standard therapy, i.e. RCT [2]. In contrast to other malignancies, no substantial progress in the treatment of ASCC has been made since implementation of RCT in the 1980s [27]. Importantly, the addition of either induction, or consolidation chemotherapy to primary RCT, concurrent chemotherapy other than MMC/5-FU, or any dose escalation of radiotherapy, failed to improve the clinical outcome as shown in large phase III trials [2,3,28]. The optimal timing for combination of CRT with immunotherapies still remains unclear. In line to preclinical evidence [13], the post hoc analysis of the PACIFIC trial [19] suggests that starting the durvalumab within 14 days after CRT (rather than $\geq$14 days) is associated with a higher benefit to OS and PFS. As such, we hypothesized that administration of Durvalumab before CRT could, potentially, prime the immune system towards a more immunogenic phenotype to facilitate increased response to CRT. This consisted the rationale for the combination schedule in our trial.

Recently, PD-1/PD-L1 pathway blockade proved to be a feasible and efficient treatment for recurrent/metastatic ASCC [8,9]. The response rate to this treatment was between 17% and 24%, and some responses were long-lasting, despite the advanced stage of the tumors treated and the negative selection due to progression after first-line therapy. So far, there is no reliable predictive marker for response to PD-1/PD-L1 blockade available. In this trial, the efficacy and toxicity of a combined RCT and PD-L1 blockade will be studied. It is expected that toxicity will be tolerable as data so far do not show any exceptional or unexpected toxicities by the combination of RT and PD-1/PD-L1 blockade [29–31]. Another novelty in this trial compared to most other trials in ASCC is the inclusion of HIV positive patients, if they are on a stable medication without measurable viral load and adequate CD4 counts as defined per protocol. The current NCCN guidelines also state that patients living with HIV should be treated with standard RCT [26]. With regard to possible side effects of immune checkpoint inhibition in this cohort, a recent study with the PD-1 inhibitor Pembrolizumab in HIV positive patients showed an acceptable safety profile [32]. With regard to efficacy, immunohistochemical and gene expression analysis revealed no differences in the composition of the tumor microenvironment between HIV positive and negative patients [33].

As standard MMC/5-FU-based RCT for ASCC is safely used for over 30 years, the main risks of the combination with durvalumab in this trial are the possible immunological toxicities attributed to durvalumab. However, the safety of durvalumab has already been tested in many published clinical trials and for various indications. Common toxicities were diarrhea, fatigue, vomiting, pain and skin reactions. Serious adverse events occurred in less than 5% of the treated patients. Intensity-modulated RT-techniques lower toxicity rates in modern series; especially the frequency of enteritis is relatively low. In retrospective studies, no increase in severe toxicities occurred following combination of RT with either CTLA-4 blockade, PD-1 blockade or PD-L1 blockade [34]. Importantly, in the recent PACIFIC phase III randomized trial in NSCLC, the combination of RCT with durvalumab was well-tolerated without any significant increase in the incidence of serious adverse effects compared to control arm that received RCT plus placebo (Grade 3–4 pneumonitis: 3.4% vs 3%; dyspnea 1.5% vs 2.6%; diarrhea 0.6% vs 1.3%; hypothyroidism: 0.2% vs 0%; fatigue 0.8% vs 1.3%) [19,35]. Adverse events leading to death were seen in 4.4% of patients given durvalumab and 5.6% of those given placebo [35].

We decided to use 26 weeks as timepoint for the evaluation of clinical response based on the findings of the ACT2 trial [36]. In that trial, clinical response was assessed prospectively 11, 18 and 26 weeks after initiation of RCT in patients with ASCC. In total, n = 691 patients attended all three assessments, and a cCR was observed in 64%, 80% and 85% at 11, 18 and 26 weeks, respectively, indicating a delayed tumor response. As expected, patients with cCR at 26 weeks post-RCT initiation had a superior 5-year

OS compared to patients without cCR. Thus, these results provided high-level evidence to justify 26 weeks after initiation of RCT (i.e. 20 weeks after completion of RCT) as the ideal time point for evaluating clinical response after RCT.

Routine testing for PD-L1 expression will not be routinely performed to enroll patients but will be assessed as part of an extensive translational research program of the RADIANCE trial. The correlation between PD-L1 expression and efficacy remains a topic of discussion. Several studies have indicated that patients can benefit from PD-L1 immune checkpoint inhibition independently of the baseline PD-L1 expression in primary tumor [37,38]. Similarly, in the phase 3 randomized trial that tested durvalumab with RCT in NSCLC, the PFS benefit was observed irrespectively of PD-L1 expression [19]. In addition, high mutational burden (e.g., in bladder carcinoma [39]) or viral tumor etiology that is linked with an activated immune response as seen in anal cancer [5] may contribute to the responses seen with immune therapy.

In conclusion, the RADIANCE trial will assess whether the combination of RCT with immunotherapy using durvalumab may improve tumor control and long-term clinical outcome in patients with locally advanced ASCC compared to RCT alone.

Ethics approval and consent to participate

The study protocol (v. 2.0, 31.10.2019) and informed constent form have been reviewed and approved by the local ethics committee of the Goethe University Frankfurt (19-374-AMG) and the responsible German federal institute for vaccines and biomedicines (Paul Ehrlich Institute).

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Trial registration

EudraCT: 2018-003005-25; ClinicalTrials.gov: NCT04230759; Date of registration: 15.01.2020.

Declaration of Competing Interest

The trial is funded by the German Cancer Aid (Deutsche Krebshilfe, DKH; Funding Project Number: 70113615; PI: Emmanouil Fokas). The study drug and the pharmacy costs (Funding Project Number: ESR-17-13077) are provided by Astra Zeneca. The authors have no further conflicts of interest to declare.

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