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Original Research

Avelumab–cetuximab–radiotherapy versus standards of care in locally advanced squamous-cell carcinoma of the head and neck: The safety phase of a randomised phase III trial GORTEC 2017-01 (REACH)

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KEYWORDS
Avelumab-cetuximab-radiotherapy;
Locally advanced squamous cell carcinoma;

Abstract ***Background:*** Based on the hypothesis of synergistic effect of avelumab with cetuximab and radiotherapy, this new combination is tested in a randomised trial against two well-established standard of care (SOC) in locally advanced squamous-cell carcinoma of the head and neck (LA-SCCHN).
Methods: This phase III trial comprises two cohorts of patients deemed fit to receive cisplatin (100 mg/m^2 Q3W) (cohort 1) or unfit to cisplatin (cohort 2). The SOC was Intensity

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Head and neck;
Safety phase

Modulated Radiation Therapy (IMRT) with cisplatin in cohort 1 (arm A) and with weekly cetuximab in cohort 2 (arm D). In both cohorts, experimental arms (arms B and C) were IMRT with cetuximab and avelumab (10 mg/kg day 7 and every 2 weeks) followed by avelumab every two weeks for 12 months. A safety phase was planned among the first 41 patients in experimental arms by monitoring grade ≥IV adverse events (AEs) with an unacceptable rate of 35%.

Results: Between September 2017 and August 2018, 82 patients with LA-SCCHN were randomised including 41 patients in experimental arms. All patients of experimental arms except one (arm C) received entire radiotherapy as planned. Most common grade ≥III AEs were mucositis, radio-dermatitis, and dysphagia. Grade ≥IV AEs occurred in 5/41 (12%) patients, all in arm C (no grade V). This rate was acceptable according to the hypotheses of the safety phase. In the SOC arms, grade ≥IV AEs occurred in 3/21 patients (14%) in arm A and 2/20 (10%) in arm D. One grade V haemorrhage occurred in arm A.

Conclusion: The avelumab–cetuximab–RT combination was tolerable for patients with LA-SCCHN, and the approval was given for continuing the trial without modification.

Clinicaltrial.gov: NCT02999087.

1. Introduction

Concurrent chemoradiotherapy (CRT) has been established as a standard of care (SOC) in non-operated patients with locally advanced squamous-cell carcinoma of the head and neck (LA-SCCHN) [1]. The most widely used standard regimen in this setting is combination of radiotherapy (RT) plus concomitant high-dose (HD) cisplatin (100 mg/m^2 every 3 weeks). Although associated with increased survival compared with RT alone, this combination is also associated with increased toxicity. In addition, a proportion of patients with LA-SCCHN are not suitable for HD cisplatin–based CRT, either due to their age or to their general and/or medical condition(s). An alternative SOC has been established with a more favourable toxicity profile by combining RT and cetuximab [2], which showed improved survival compared with RT.

However, these two SOCs are both associated with a relatively important failure rate especially in patients with advanced tumours, suggesting a strong medical need for developing new approaches to improve both tolerance and treatment efficacy. Interestingly recent data from the GORTEC 2007–01 trial showed a clinical benefit associated with treatment intensification added to cetuximab-RT [3]. This study provided a rational for using this cetuximab–RT combination as a backbone and adding a new type of intensification that could potentially be more effective and/or better tolerated than the concurrent chemotherapy component added in this GORTEC trial.

Recently, PD-1/PD-L1 inhibitors demonstrated promising results in SCCHN [4]. Avelumab selectively binds to PD-L1 and competitively blocks its interaction with PD-1 that has durable antitumour activity and a tolerable safety profile in a range of solid tumours [5]. The most frequent (>6%) treatment-related adverse events (AEs) were fatigue, infusion-related reaction, nausea, diarrhoea, chills, and pyrexia [6]. Avelumab is the only PD-1/PD-L1 inhibitor that can induce antibody-dependent cell-mediated cytotoxicity (ADCC). This could be of particular interest to synergise with the ADCC induced by cetuximab, which is supposed to be a key determinant of its antitumour activity [7]. A strong body of evidence supports the combination of RT with immunotherapy such as a PD-1/PD-L1 inhibitor [8,9]. In addition, the overall response to avelumab in the second line of recurrent/metastatic SCCHN is similar to that of pembrolizumab or nivolumab. There is a strong rational for testing the addition of avelumab to cetuximab–RT against the two well-established SOC in LA-SCCHN due to the unmet medical need for new SOC well tolerated and equally or more effective than both CRT or cetuximab–RT. However, very little was known regarding the AE of this combination. We report here the results of the safety phase of the phase III GORTEC 2017-01 REACH trial with particular focus on skin toxicity.

2. Methods

2.1. Study design and participants

This is an open-label, randomised, multicenter phase III study for patients with LA-SCCHN run in France, Monaco and Switzerland. The study protocol was approved by national ethics committees and institutional review boards. The study was done in accordance with the Declaration of Helsinki. All patients provided written informed consent. The primary objective was to compare, in terms of progression-free survival (PFS), the treatment with avelumab–cetuximab–RT to that

with the SOC cisplatin–RT in patients fit to receive HD cisplatin or to that with the SOC cetuximab–RT in patients unfit to receive HD cisplatin.

Inclusion criteria were as follows: 18–80 years; performance status (PS) Eastern Cooperative Oncology Group (ECOG), 0–1; histologically confirmed squamous-cell carcinoma, previously untreated stage III/IV (the American Joint Committee on Cancer 7th edition), the primary location in the oral cavity, oropharynx, hypopharynx or larynx; the known p16 status for oropharyngeal cancer (OPC).

Criteria for determination of the patient's ability to receive HD cisplatin were as follows: creatinine clearance ≥60 mL/min (CKD-EPI method); absolute neutrophil count ≥1500/μL; platelet count ≥100000/μL; haemoglobin ≥10 g/dL; ASAT (aspartate aminotransférases) and ALAT (alanine aminotransférases) < 2 × ULN; total bilirubin ≤1.5 mg/dL; serum albumin >35 g/L; peripheral neuropathy < grade II; hearing loss < grade II; cardiac function compatible with hyperhydration; age < 75 years (if 71–74 years, patients must have PS ECOG 0 and considered fit by geriatric evaluation). Patients fit to receive HD cisplatin were included in cohort 1 with cisplatin–RT as SOC; patients unfit to receive HD cisplatin were included in cohort 2 with cetuximab–RT as SOC.

2.2. Randomisation

Patients were randomised in a 1:1 ratio to either arm A (cisplatin–RT) or B (avelumab–cetuximab–RT) in cohort 1 (fit for HD cisplatin); or in a 1:1 ratio to either arm C (avelumab–cetuximab–RT) or D (cetuximab–RT) in cohort 2 (unfit for HD cisplatin). Treatment allocation was done by minimisation on the following factors: centre, nodal stage (N0/N1 versus N2/N3) and p16 status (OPC p16+ versus OPC p16− or non-OPC). The investigators and delegated site staff perform randomisation directly by internet with a secured connection.

2.3. Procedures

2.3.1. There were three treatment phases

The lead-in phase on day 7 before RT: in arms B and C, single dose of avelumab (10 mg/kg) was delivered; in arms B, C and D, single dose of cetuximab 400 mg/m^2 was given.

The concomitant RT phase: in arm A, cisplatin 100 mg/m2 on days 1, 22 and 43; in arms B and C, avelumab 10 mg/kg was given every 2 weeks (Q2W); in arms B, C and D, cetuximab 250 mg/m^2 was given weekly.

The maintenance phase (after RT): in arms B and C, avelumab 10 mg/kg dosage was started 2 weeks after the end of RT and then Q2W for 12 months. Arms A and D had no maintenance.

RT was performed using Intensity Modulated Radiation Therapy (IMRT), with a simultaneous integrated boost technique. RT to high-risk CTV (Clinical Target Volume) was delivered daily (2.12 Gy/fraction) for 5 days/week to 69.96 Gy over 6.5 weeks (33 fractions). The low risk CTV received 52.8 Gy in 33 fractions.

2.4. Safety endpoints

Acute AEs and laboratory abnormalities were graded as per the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03. The safety monitoring was based on acute AEs defined as AEs occurring during the first 8 weeks of treatment, i.e. the lead-in phase and the concomitant RT phase.

2.5. Data quality

A bi-monthly toxicity review was done by the trial Steering Committee with investigators from individual sites. The sponsor monitors carried out a 100% monitoring of the safety data of all patients entered in the eCRF.

2.6. Statistical analysis

In cohort 1, the expected hazard ratio (HR) with avelumab–cetuximab–RT versus cisplatin–RT is 0.64, corresponding to a difference of 15% in three-year PFS (45%–60%). Assuming a two-sided type I error of 0.05, observing 166 events will provide an 80% power. Four hundred and twenty patients (210 per arm) will be randomised. In cohort 2, the expected HR with avelumab–cetuximab–RT versus cetuximab–RT is 0.62, corresponding to a gain of 17% in three-year PFS (40%–57%). Assuming a one-sided type I error of 0.05, observing 115 events will provide an 80% power. Two hundred and sixty-eight patients (134 per arm) will be randomised.

An early safety phase was planned by monitoring the rate of grade ≥IV acute AEs among the first 41 patients treated in the two experimental arms together. As in the recent GORTEC randomised trials the rate of grade ≥IV acute AEs was around 18% in the concomitant CT–RT arms and 15% in the cetuximab–RT arm, we set the reference rate of grade ≥IV acute AEs at 15%. The unacceptable rate was set at 35%. The analyses were planned in three steps, on 14, 27 and 41 patients treated in the experimental arms. Safety data from each patient were continuously collected. The bounds to declare toxicity as too excessive were ≥7 patients with grade ≥IV acute AEs among 14 patients at the first step, ≥8/27 at the second step and ≥10/41 at the third step. The global one-sided α error was 0.09 and β error 0.05. With the chosen unacceptable rate of patients with grade ≥IV AEs, the trial will continue after the safety study only if there are nine or less patients with grade ≥IV AEs

Table 1
Patient and disease initial characteristics.

Characteristics	Arm A n = 21	Arm B n = 21	Arm C n = 20	Arm D n = 20	Total N = 82
Female	1 (5%)	1 (5%)	8 (40%)	1 (5%)	11 (13%)
Male	20 (95%)	20 (95%)	12 (60%)	19 (95%)	71 (87%)
Age (mean [range]) years	56.1 [40; 72]	57.5 [49; 69]	67.6 [54; 78]	64.8 [54; 78]	61.4 [40; 78]
ECOG					
0	10 (48%)	13 (62%)	9 (45%)	11 (55%)	43 (52%)
1	11 (52%)	8 (38%)	11 (55%)	9 (45%)	39 (48%)
Smoking status					
Never smoker	0 (0%)	3 (14%)	6 (30%)	3 (15%)	12 (15%)
Former smoker	13 (62%)	10 (48%)	7 (35%)	13 (65%)	43 (52%)
Current smoker	8 (38%)	8 (38%)	7 (35%)	4 (30%)	27 (33%)
Subsite					
Oropharynx	16 (76%)	15 (71%)	14 (70%)	15 (75%)	60 (73%)
Hypopharynx	3 (14%)	5 (24%)	3 (15%)	3 (15%)	14 (17%)
Oral cavity	1 (5%)	0 (0%)	1 (5%)	1 (5%)	3 (4%)
Larynx	1 (5%)	1 (5%)	2 (10%)	1 (5%)	5 (6%)
Oropharynx p16 positive	8 (38%)	7 (33%)	7 (35%)	6 (30%)	28 (34%)
Stage					
III	2 (10%)	3 (14%)	2 (10%)	7 (35%)	14 (17%)
IVa	15 (71%)	13 (62%)	17 (85%)	8 (40%)	53 (65%)
IVb	4 (19%)	5 (24%)	1 (5%)	5 (25%)	15 (18%)

ECOG, Eastern Cooperative Oncology Group.

among 41 patients, i.e. if the observed rate of patients with grade ≥IV AEs is ≤ 22% (90% confidence interval of this rate = 12%–35%). The results of the three safety analyses were presented and reviewed by the Independent Data and Safety Monitoring Committee (IDSMC) of the trial. The toxicity observed in the SOC arms A and D was also presented for complete information on the trial safety.

4. Results

Between September 2017 and August 2018, 83 patients with stage III/IV SCCHN were randomised in the trial (Fig. 1). One patient in arm C withdrew consent before treatment started and was excluded from all analyses. The safety analyses are based on 41 patients in experimental arms (21 in arm B and 20 in arm C).

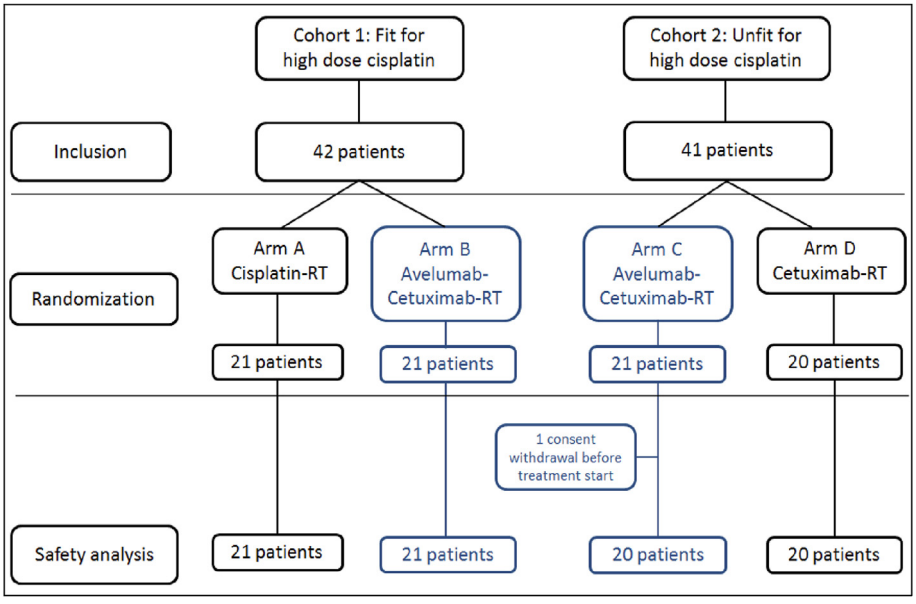

Fig. 1. Trial profile.

Table 2
Radiotherapy compliance.

Characteristics	Arm A n = 21	Arm B n = 21	Arm C n = 20	Arm D n = 20
IMRT administered	21 (100%)	21 (100%)	20 (100%)	20 (100%)
69.96 Gy	21 (100%)	21 (100%)	19 (95%)	19 (95%)
Other dose	0 (0%)	0 (0%)	1 (55.1 Gy, stop due to digestive perforation and heart failure)	1 (80.6 Gy, interruption of 2 months due to pneumonia)
Interruption > 5 consecutive days or duration>49 days	1 (5%)	3 (14%)	3 (15%)	4 (20%)
Reason	Haematoma grade III	Atrioventricular block grade III Parotitis and peritonsillar abscess grade III Tracheal obstruction (3 times)	Digestive perforation grade IV Pt general condition (mucositis grade 3 + hypotension grade III), Constipation grade II	1 infectious pneumonia grade IV 1 peritonitis grade IV 2 dermatitis (grade II and grade III)

IMRT, Intensity Modulated Radiation Therapy.

Characteristics and safety of the 41 patients of the SOC arms (21 in arm A and 20 in arm D) are also presented.

4.1. Initial characteristics (Table 1)

Seventy one of 82 (87%) were male, 95% in cohort 1 and 78% in cohort 2. The mean age was 56.8 years in cohort 1 and 66.2 in cohort 2. All patients were ECOG 0–1 with 43/82 (52%) ECOG 0. Only 12/82 patients (15%) were never smokers, 7% in cohort 1 and 23% in cohort 2. The site of carcinoma was the oropharynx in 60/82 patients (73%), and 28/82 (34%) were p16 positive. All patients were stage III and IV, among which 53/82 (65%) with IVa and 15/82 (18%) with IVb.

4.2. Compliance to treatment (Table 2)

All patients were treated with IMRT, and all except one (arm C) received the total number of planned RT fractions and 69.96 Gy. One patient of arm C had definitive interruption of RT after 55 Gy because of patient's refusal following grade IV gastrointestinal perforation. Interruption >5 consecutive days or duration >49 days were seen in 1, 3, 3 and 4 patients of arms A, B, C and D, respectively.

The compliance to concurrent cisplatin in arm A was as usually observed in this setting [10]: 76% patients (16/21) received three cycles, 19% (4/21) two cycles and 5% (1 patient) only one cycle. The mean percentage received of the theoretical dose was 86% (34%; 102%). The rate of patients who received at least seven cycles of cetuximab was 90% (19/21 patients) in arm B (cohort 1) and 80% (16/20 patients) and 85% (17/20 patients) in arms C and D (cohort 2). In the experimental arms, 95% patients (20/21) received all planned administrations of lead-in and concurrent avelumab in arm B (cohort 1) and 80% (16/20 patients) in arm C (cohort 2).

4.3. Adverse events (Tables 3 and 4)

In the analysis of the 82 patients, at least one AE of any grade occurred in all patients of each arm. The rates of patients with at least one grade III AE were 86%, 85% and 95% in arms A, B + C and D, respectively. The rates of patients with at least one grade IV AE were 10% (2/21), 12% (5/41) and 10%

Table 3
Number (%) of patients with adverse events by grade in experimental and SOC arms.

Characteristics	Arm A (SOC cisplatin)	Arms B + C (experimental)	Arm D (SOC cetuximab)
Any grade	21 (100%)	41 (100%)	20 (100%)
Grade I	20 (95%)	39 (95%)	20 (100%)
Grade II	20 (95%)	41 (100%)	16 (80%)
Grade III	18 (86%)	35 (85%)	19 (95%)
Grade IV	2 (10%)	5 (12%)	2 (10%)
Grade V	1 (5%)	0 (0%)	0 (0%)

SOC, standard of care.

Table 4
Adverse events in the experimental arms B and C (avelumab, cetuximab and radiation) that occurred in more than 5% of patients or with grade ≥III.

Characteristics	All		Grade I		Grade II		Grade III		Grade IV	
	N	%	N	%	N	%	N	%	N	%
Any AE	41	100%	39	95.1%	41	100%	35	85.4%	5	12.2%
Mucositis oral	40	97.6%	3	7.3%	16	39.0%	21	51.2%	1	2.4%
Dermatitis radiation	39	95.1%	7	17.1%	11	26.8%	20	48.8%	1	2.4%
Dysphagia	34	82.9%	7	17.1%	11	26.8%	16	39.0%	0	
Rash acneiform	32	78.0%	14	34.1%	16	39.0%	2	4.9%	0	
Xerostomia	25	61.0%	16	39.0%	8	19.5%	1	2.4%	0	
Fatigue	17	41.5%	10	24.4%	6	14.6%	1	2.4%	0	
Weight loss	15	36.6%	10	24.4%	5	12.2%	0		0	
Oral pain	13	31.7%	6	14.6%	4	9.8%	3	7.3%	0	
Dysgeusia	13	31.7%	7	17.1%	6	14.6%	0		0	
Nausea	11	26.8%	8	19.5%	2	4.9%	1	2.4%	0	
Lymphopenia	10	24.4%	1	2.4%	3	7.3%	5	12.2%	1	2.4%
Constipation	8	19.5%	6	14.6%	2	4.9%	0		0	
Dry skin	8	19.5%	5	12.2%	3	7.3%	0		0	
Fever	8	19.5%	6	14.6%	2	4.9%	0		0	
Hypoalbuminemia	6	14.6%	1	2.4%	4	9.8%	1	2.4%	0	
Anemia	6	14.6%	5	12.2%	0		0		1	2.4%
Pain	6	14.6%	2	4.9%	4	9.8%	0		0	
Anorexia	5	12.2%	3	7.3%	1	2.4%	1	2.4%	0	
Aspartate aminotransferase	5	12.2%	4	9.8%	0		1	2.4%	0	
Alanine aminotransferase increased	5	12.2%	4	9.8%	1	2.4%	0		0	
Hypomagnesemia	5	12.2%	3	7.3%	1	2.4%	1	2.4%	0	
Hypophosphatemia	5	12.2%	1	2.4%	3	7.3%	1	2.4%	0	
Vomiting	5	12.2%	3	7.3%	1	2.4%	1	2.4%	0	
Diarrhea	5	12.2%	4	9.8%	1	2.4%	0		0	
Esophagitis	4	9.8%	1	2.4%	2	4.9%	1	2.4%	0	
Cough	4	9.8%	3	7.3%	1	2.4%	0		0	
Headache	4	9.8%	4	9.8%	0		0		0	
Palmar–plantar erythrodysesthesia syndrome	4	9.8%	2	4.9%	2	4.9%	0		0	
Catheter infection	3	7.3%	0		0		3	7.3%	0	
Allergic reaction	3	7.3%	0		2	4.9%	1	2.4%	0	
Cheilitis	3	7.3%	1	2.4%	1	2.4%	1	2.4%	0	
GGT increased	3	7.3%	1	2.4%	1	2.4%	1	2.4%	0	
Serum amylase increased	3	7.3%	2	4.9%	0		1	2.4%	0	
Tumour pain	3	7.3%	1	2.4%	1	2.4%	1	2.4%	0	
Back pain	3	7.3%	0		3	7.3%	0		0	
Odynophagia	3	7.3%	0		3	7.3%	0		0	
Pruritus	3	7.3%	2	4.9%	1	2.4%	0		0	
Tinnitus	3	7.3%	3	7.3%	0		0		0	
Voice alteration	3	7.3%	1	2.4%	2	4.9%	0		0	
Dyspnea	2	4.9%	0		0		2	4.9%	0	
Trismus	2	4.9%	0		1	2.4%	1	2.4%	0	
Gastrointestinal perforation	1	2.4%	0		0		0		1	2.4%
Acute bronchitis	1	2.4%	0		0		1	2.4%	0	
Arterial pressure decreased	1	2.4%	0		0		1	2.4%	0	
Atrioventricular block	1	2.4%	0		0		1	2.4%	0	
Dehydration	1	2.4%	0		0		1	2.4%	0	
Eye injury	1	2.4%	0		0		1	2.4%	0	
Parotitis	1	2.4%	0		0		1	2.4%	0	
Peritonsillar abscess	1	2.4%	0		0		1	2.4%	0	
Radiation vasculitis	1	2.4%	0		0		1	2.4%	0	
Rectal bleeding	1	2.4%	0		0		1	2.4%	0	
Renal insufficiency	1	2.4%	0		0		1	2.4%	0	
Skin bleeding	1	2.4%	0		0		1	2.4%	0	

AE, adverse event; GGT, Gamma-GT (Gamma Glutamyl-Transferase).

Table 5
Skin toxicity in experimental and SOC arms.

Characteristics	Arm A (SOC cisplatin)	Arms B + C (experimental)	Arm D (SOC cetuximab)
	(N = 21)	(N = 41)	(N = 20)
Radiation Dermatitis			
Grade I	11 (52%)	8 (20%)	1 (5%)
Grade II	7 (33%)	11 (27%)	7 (35%)
Grade III	4 (19%)	20 (49%)	11 (55%)
Grade IV	0	1 (2%)	0
Rash acneiform/maculo-papular			
Grade I	0	15 (37%)	7 (35%)
Grade II	0	16 (39%)	6 (30%)
Grade III	0	2 (5%)	3 (15%)
Grade IV	0	0	0
Erythema			
Grade I	1 (5%)	1 (2%)	0
Grade II	0	2 (5%)	0
Grade III	0	0	0
Dry skin			
Grade I	0	5 (12%)	1 (5%)
Grade II	0	3 (7%)	0
Skin infection			
Grade I	0	0	1 (5%)
Grade II	0	1 (2%)	0
Vitiligo			
Grade I	0	1 (2%)	0

SOC, standard of care.

(2/20) in arms A, B + C and D, respectively. One hemorrhagic grade V AE occurred in arm A.

In the experimental arms (B + C, 41 patients), the most common AEs of any grade were mucositis (40 patients), radio-dermatitis (39 patients), dysphagia (34 patients) and rash (32 patients), and the most common grade ≥III AEs were mucositis (21 patients), radio-dermatitis (20 patients) and dysphagia (16 patients) (Table 3). Other grade ≥III AEs with incidence >5% included decrease of the lymphocyte count (six patients), catheter-related infection (three patients) and oral pain (three patients) (Table 3).

4.4. Monitoring of adverse events of grade ≥IV

At the first step of safety analysis, the number of patients treated in the experimental arms B + C with at least one grade ≥IV acute AE was 3/14; at the second step it was 3/27, and at the third step, 5/41. The bounds for excessive toxicity were not crossed at any of the three steps, and the IDSMC members recommended continuing the trial after each analysis.

In arm B of cohort 1, no patient had AEs of grade ≥IV. In arm C of cohort 2, five of 20 patients had an AE of grade IV: one radio-dermatitis, one mucositis, one non-clinically significant lymphopenia, one anaemia due to colon polyp bleeding and one gastrointestinal perforation on an old ileo-colic anastomosis. No grade IV AE occurred in the experimental arms. The characteristics of the five patients who suffered from grade ≥IV AEs in this arm seemed not different from those of the 15 other patients of this arm: 60% male versus 60%, mean age 68 years versus 67 years, 40% PS ECOG 1 versus 60%, 40% current smoker versus 33%, 60% oropharyngeal tumour versus 73% and 100% stage IV versus 87%.

In arm A, one patient had a hemorrhagic grade V AE leading to cardiopulmonary arrest and two patients had grade IV AEs (one dysphagia and one neutropenia and lymphopenia). In total, three of 21 patients (14%) had grade ≥IV AE.

In arm D, two patients had grade IV AEs (one pneumonia and eschar and one peritonitis after percutaneous endoscopic gastrostomy insertion).

4.5. Skin toxicity (Table 5)

We observed grade ≥III radio-dermatitis in 4/21 patients (19%) of arm A, 21/41 (51%) in arms B + C and 11/20 (55%) in arm D. Only one grade IV radio-dermatitis was observed, in one patient of arm C.

Rash grade III was observed in 2/41 patients (5%) in arms B + C and 3/20 (15%) in arm D, whereas none was observed in arm A.

5. Discussion

The safety phase of the REACH study was based on 41 patients treated by avelumab–cetuximab–RT in the experimental arms B and C. Acute AEs of grade ≥IV occurred in five patients, i.e. a rate of 12% (90% CI = 5%–24%) which was similar to the historical rates observed in SOC arms (18% in the CRT arms and 15% in the cetuximab–RT arm in the previous GORTEC trials). In the cohort 1 (21 fit patients of arm B), the avelumab–cetuximab–RT was well tolerated without grade IV AEs. Grade IV AEs were observed in five of the 20 unfit patients of the cohort 2 treated with avelumab–cetuximab–RT (arm C). There was no treatment-related death during the concurrent treatment phase even for patients of the cohort 2, whereas one death occurred in the arm A (cisplatin–RT). Nevertheless, we should still give great attention to the patients of the experimental arm in cohort 2 (arm C) to avoid potential severe toxicity. In the experimental arms, most frequent grade ≥III acute AEs were mucositis, radio-dermatitis and dysphagia, and this is consistent with toxicities induced by chemo-radiotherapy or cetuximab–RT [3]. A good compliance to radiotherapy was observed in the experimental arms.

The combination of PD-1/PD-L1 inhibitors and radiation has been shown to be safe in several recent studies [9,11]. Concurrent pembrolizumab–RT had lower rate of severe AEs than cetuximab–RT in our recent GORTEC 2015–01 PembroRad randomised

phase II trial [11]. Adjuvant durvalumab has been shown to improve survival of patients with non–small cell lung cancers after conventional CRT in the PACIFIC trial [9]. The combination of avelumab with targeted therapy maybe a promising cancer treatment. Recently, avelumab combined with axitinib has shown a better PFS compared to sunitinib in renal-cell carcinoma [5]. However, up to now, there was no prospective trial evaluating the safety and efficacy of the combination of avelumab, cetuximab and radiation. Several randomized phase III trials are ongoing evaluating the combination of PD-1/PD-L1 inhibitors (pembrolizumab, avelumab, etc.) with RT/CRT in LA-SCCHN, and the GORTEC REACH trial is the first phase III trial evaluating the combination of radiotherapy with concurrent avelumab and cetuximab versus SOC in LA-SCCHN.

The most reported AE which could limit the treatment is skin toxicity especially radio-dermatitis becauseRT and cetuximab alone could induce serious radiodermatitis [3,12]. Avelumab and cetuximab have been shown to enhance high affinity natural killer cells killing of SCCHN cells via ADCC [13]. Avelumab appears appealing to be combined with cetuximab for the treatment of SCCHN because avelumab not only inhibits PD1/PD-L1 interactions but also by retaining a native Fc-region can engage the innate immune system and may induce ADCC [7]. This effect could not only potentially increase the tumour control, but also aggravate the skin toxicities especially serious radiodermatitis. We did observe more severe radiodermatitis in arms B + C than in arm A with cisplatin–RT, but the grade ≥III radio-dermatitis had not been increased by avelumab when compared with RT and cetuximab alone (arm D). Other skin toxicities such as rash were also similar between the arms B + C and D. Thus, avelumab would probably not increase skin toxicities induced by cetuximab–RT.

No serious unexpected toxicity related to avelumab was observed in this safety phase of the REACH trial, nor increase of immune-related (Ir) AEs, but more follow-up is needed because some of the IrAEs could appear during the maintenance phase within one-year period of treatment with avelumab. The trial is ongoing, and we could not yet analyse long-term toxicity or treatment efficacy of this combination of avelumab and cetuximab with RT compared with cisplatin–RT or cetuximab–RT.

In conclusion, the combination of avelumab, cetuximab and RT was safe for patients with LA-SCCHN, and IDSMC and the health authorities gave approval for continuing the study without modification after this safety phase. Attention need to be paid to toxicities of patients in the unfit cohort. The accrual is currently ongoing at a rate of around 30 patients per month.

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Conflict of interest statement

All authors declare no conflict of interest.

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