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Original Research

Patritumab or placebo, with cetuximab plus platinum therapy in recurrent or metastatic squamous cell carcinoma of the head and neck: A randomised phase II study

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KEYWORDS
Patritumab;
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Recurrence;
Metastatic;
Squamous cell carcinoma of the head and neck;

Abstract ***Background:*** The fully human monoclonal antibody patritumab blocks HER3 activation, a resistance mechanism to cetuximab, induced by heregulin (HRG). A phase Ib study in recurrent and/or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN) demonstrated tolerability and tumour response of patritumab + cetuximab + platinum.
Methods: This was a randomised, double-blind, phase II study of patritumab + cetuximab with platinum-based therapy for first-line treatment of R/M SCCHN (Clinicaltrials.gov identifier: NCT02633800). Patients aged ≥18 years received patritumab or placebo, both combined with cetuximab + cisplatin or carboplatin. Co-primary end-points were progression-free survival (PFS) in the intent-to-treat (ITT) and the high-expression HRG (HRG high) populations.

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Clinical trial;
Phase II

Results: Eighty-seven patients ($n = 43$ in the patritumab group; $n = 44$ in placebo group) enrolled. A median (range) of 6.5 (1–24) patritumab cycles were completed. Median PFS was similar between the patritumab group and placebo group in the ITT population (5.6 versus 5.5 months; hazard ratio [HR] 0.99 [95% confidence interval [CI], 0.6–1.7]; $P = 0.96$) and HRG-high subgroup ($n = 51$; 5.6 versus 5.6 months; HR 0.93 [95% CI, 0.5–1.8]; $P = 0.82$). Median overall survival in the ITT population was also similar (10.0 versus 12.7 months; HR 1.3 [95% CI, 0.69–2.29]; $P = 0.46$). All patients experienced ≥1 treatment-emergent adverse event (TEAE). Grade ≥III TEAEs were more frequent in the patritumab than the placebo group (84.1% versus 60.5%). The most common grade ≥III patritumab-related TEAE in the patritumab group (20.5% overall) was rash (6.8%).
Conclusion: Patritumab + cetuximab + platinum was tolerable but not superior to cetuximab + platinum.

1. Introduction

Over 90% of cancers of the head and neck are squamous cell cancers, with approximately 600,000 cases diagnosed worldwide each year [1,2]. Patients typically present with advanced disease and standard-of-care is concomitant locoregional treatment and chemotherapy [3]. However, the recurrence rate in locally advanced disease is approximately 50% [4].

The EXTREME regimen (non-nasopharyngeal) or cisplatin and gemcitabine (nasopharyngeal) are recommended by the National Comprehensive Cancer Care Network (NCCN) guidelines as category 1 first-line combination treatment for recurrent and/or metastatic (R/M) of squamous cell carcinoma of the head and neck (SCCHN) [5]. There is currently no category 1 single-agent therapy for first-line treatment, though second-line single-agent treatment with programmed cell death protein 1 inhibitors nivolumab (category 1) or pembrolizumab (category 2a) are recommended for non-nasopharyngeal R/M SCCHN. The EXTREME regimen consists of a platinum agent (cisplatin or carboplatin) plus 5-fluorouracil chemotherapy and the epidermal growth factor receptor (EGFR) inhibitor cetuximab, which has been shown to enhance the anti-tumour activity of platinum-based chemotherapy [6]. Patients who initially respond to cetuximab-based therapy may later develop resistance [7,8].

A possible mechanism of cetuximab resistance is upregulation of HER3 expression [7]. Elevated membranous HER3 expression is also strongly associated with poor prognosis in patients with SCCHN [9]. There is growing evidence that the presence of heregulin (HRG), a natural ligand for HER3, determines disease progression and patient survival in SCCHN [10,11]. Patritumab is a fully human HER3 monoclonal antibody that binds to the extracellular domain of HER3, promoting receptor internalisation and degradation, and inhibiting ligands from binding HER3—including HRG [12,13]. HER3 signalling is associated with high expression of HRG [10] and shown to be important for tumour growth and proliferation, including in non-small cell lung cancer [14] and SCCHN cell lines and in animal models [15]. When combined with EGFR inhibitors, including cetuximab and panitumumab, patritumab enhanced *in vitro* antitumour activity and prevented HER3 activation following anti-EGFR treatment [12,13,15].

In preclinical studies, patritumab restored cetuximab sensitivity in colorectal cancer, and patritumab + cetuximab resulted in a stronger inhibition of proliferation and induction of apoptosis compared with either treatment alone in patritumab-responsive SCCHN cell lines [15,16]. A phase Ib study in R/M SCCHN (clinicaltrials.gov identifier: NCT02350712) found the combination of patritumab plus cetuximab with platinum therapy to be tolerated, active in patients with R/M SCCHN and did not appear to have a significant effect on the pharmacokinetics (PKs) of cetuximab [17]. The phase I study recommended an 18 mg/kg loading dose of patritumab, followed by a 9 mg/kg maintenance dose every 21 days.

This randomised phase II study in multiple centres across Europe evaluated safety, efficacy and PKs of first-line cetuximab + cisplatin or carboplatin with either patritumab or placebo in patients with R/M SCCHN and known *HRG* expression status.

2. Material and methods

2.1. Overall study design

This was a multicentre, randomised, placebo-controlled, double-blind, phase II study of first-line treatment of patritumab plus cetuximab with platinum-based therapy in patients with R/M SCCHN (clinicaltrials.gov identifier: NCT02633800). This study was conducted in compliance with the Declaration of Helsinki, the International Conference on Harmonisation,

Guidelines for Good Clinical Practice and applicable national and local regulatory requirements. The protocol was approved by the Institutional Review Board at each study site, and all patients provided written informed consent before participation in this study. Patients were stratified 2:1 by HRG status high versus low (HRG ascertained via reverse transcriptase-PCR from tumour RNA), then randomised 1:1 to patritumab or placebo (Fig. 1).

2.2. Patient eligibility

2.2.1. Key inclusion criteria

Adults (age ≥18 years) with histologically confirmed R/M SCCHN, documented *HRG* expression (archived or fresh biopsy), measurable disease per Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1, human papillomavirus (HPV) status or p16 (HPV surrogate), Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, and with adequate haematological, renal and hepatic function were eligible for inclusion into the study. Adequate haematologic function was defined as having an absolute neutrophil count $\geq 1.5 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L and haemoglobin ≥10 g/dL. Adequate renal function was defined as having a calculated creatinine clearance ≥60 mL/min. Adequate hepatic function was defined as having an aspartate aminotransferase and alanine aminotransferase ≤2.5 × upper limit of normal (ULN) (<5 × ULN if liver metastases are present), alkaline phosphatase ≤2.0 × ULN (<5 × ULN if bone or liver metastases are present) and bilirubin ≤1.5 × ULN. Patients had prothrombin time or partial thromboplastin time ≤1.5 × ULN. Patients had to agree to comply with the contraception requirements as specified in the study protocol or be of non-childbearing potential.

2.2.2. Exclusion criteria

Patients were excluded if they had a prior EGFR-targeted regimen, anti-HER3 therapy, chemotherapy for R/M disease, anticancer therapy between biopsy and submission of sample, platinum-containing drug therapy with radiotherapy <6 months before the study, or therapeutic or palliative radiation therapy or major surgery ≤4 weeks before the study. Other exclusion criteria included left ventricular ejection fraction <50%, squamous cell tumours of the nasopharynx or a known history of active brain metastases.

2.3. Treatment

All patients received intravenous patritumab (18 mg/kg loading dose; 9 mg/kg maintenance dose every 3 weeks [q3w]) or placebo, cetuximab (400 mg/m^2 loading dose; 250 mg/m^2 maintenance dose weekly) and up to 6 cycles of cisplatin (100 mg/m^2 q3w) or carboplatin (area under the concentration curve [AUC] of 5) using the Calvert formula for optimal dosing based on renal function [18].

A patient could withdraw from study treatment or from the study at any time at their discretion. Reasons for discontinuation from the study included progressive disease (PD) per RECIST version 1.1 or clinician's assessment, adverse event (AE), withdrawal of consent, death, protocol violation or sponsor decision to terminate the study.

2.4. Study end-points

The co-primary efficacy end-points were to evaluate progression-free survival (PFS) in the intent-to-treat (ITT) and HRG-high expression populations from patients treated with patritumab + cetuximab + platinum–based therapy compared with placebo + cetuximab + platinum–based therapy. Secondary efficacy end-points included overall survival (OS), overall response rate (ORR) and safety and tolerability. Safety and tolerability end-points included treatment-emergent adverse events (TEAEs), grade ≥III TEAEs and serious AEs (SAEs). PK end-points included AUC from time 0 to last measurable concentration ($AUC_{0\text{-last}}$) and maximum concentration (C_{max}) for loading doses of patritumab and cetuximab. End-points also included the

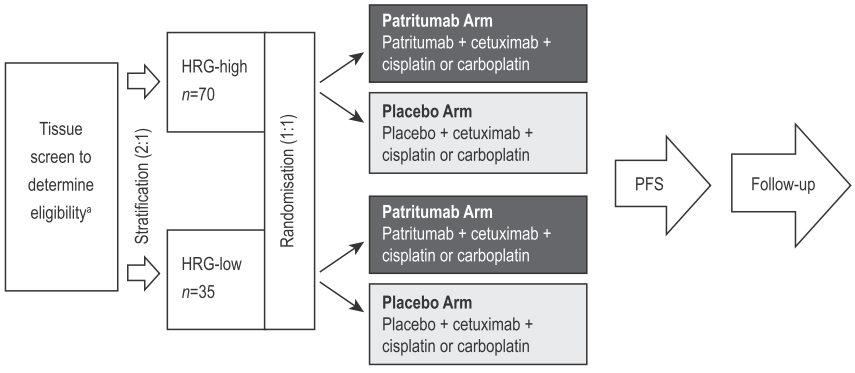

Fig. 1. Study design. HRG, heregulin; PFS, progression-free survival. [a]HRG status was determined at one timepoint only (at screening); multiple biopsies were not collected.

plasma concentration of patritumab and cetuximab and the incidence of human antihuman antibodies (HAHA). Analyses of treatment outcomes by tumour subsite were not prespecified and thus not carried out.

2.5. Study assessments

PFS was defined as the time from the treatment start date to the date of the first radiographic disease progression or death due to any cause. OS was defined as the time from treatment start date to death from any cause. Tumour response (complete response, partial response, stable disease, PD) was assessed via RECIST, version 1.1.

TEAEs were assessed per Common Terminology Criteria for Adverse Events, version 4.03, and the Medical Dictionary for Regulatory Activities, version 17.0. An SAE was defined as any untoward medical occurrence that results in death, is life threatening, results in hospitalisation or prolongs existing hospitalisation, results in a disability, is a congenital anomaly or birth defect, or is an important medical event. Patients who discontinued the study for any reason were followed for 40 days after their last dose to assess the presence of HAHA and other TEAEs. Any patients who were positive for neutralising antibodies required follow-up testing every 3 months for up to 1 year following the last dose and until titres returned to baseline or until the start of another cancer therapy.

Patient-reported outcomes were assessed using the 10-item Functional Assessment Cancer Therapy (FACT) Head and Neck Questionnaire (FACT H&N)—a multidimensional, self-report quality of life (QoL) instrument specifically designed for use with patients with head and neck cancer—and the 5-level EuroQol-5-dimensions (EQ-5D-5L) instrument. In the FACT H&N, patient well-being is assessed in four domains: functional, emotional, social and physical. Each item is rated on a 0 to 4 Likert-type scale and then combined to produce subscale scores for each domain, as well as a global QoL score. Higher scores represent better QoL. The EQ-5D-5L consists of the EQ-5D-5L descriptive system and the EuroQoL Visual Analogue scale (EQ VAS). The EQ-5D-5L descriptive system is a preference-based measure of health status comprising five domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each domain has five levels ranging from 1 (no problems) to 5 (extreme problems). The EQ VAS records the respondent's self-rated health on a 20-cm vertical VAS with end-points labelled 'the best health you can imagine' and 'the worst health you can imagine.'

2.6. Statistical considerations and analysis

A stratified log-rank test was performed to compare treatment groups for PFS. A stratified Cox proportional hazards model was used to calculate hazard ratios (HRs) and confidence intervals (CIs). Unstratified tests and models were used for HRG and HPV strata. PFS was tested in the ITT analysis set and the HRG-high stratum of the full analysis data set at a 1-sided 0.10 significance level.

Serum drug concentrations and PK parameters were summarised using descriptive statistics, and safety data were analysed descriptively. FACT H&N was evaluated using mixed longitudinal modelling with treatment, time and treatment-by-time interactions as fixed effects, patient as random effect and baseline score as covariate. Least square (LS) mean differences between the control group and patritumab group are presented along with 95% CIs.

Descriptive statistics for the actual value and change from baseline were computed for the EQ-5D-5L and EQ-5D VAS by scheduled time of evaluation (including end of treatment visit) for all patients and by treatment group.

Final analyses occurred after study closure with mature OS data (i.e. when all patients had died or $\geq$13 months after the last patient was randomised; whichever came first). After discontinuation from study treatment, follow-up information for survival was obtained per telephone approximately every 3 months for $\geq$13 months.

A quantitative real-time polymerase chain reaction (RT-PCR) assay was designed and validated (MolecularMD, Portland, Oregon; data unpublished) to quantitate *HRG* expression in commercial SCCHN tissue samples. This validated assay was then used to measure *HRG* mRNA from tumour tissue from the patients in this study and commercial tumour tissue. The cut-off for HRG high versus HRG low before patient randomisation was set using the median HRG value from commercial samples. An initial cut-off of 0.93 (delta cycle threshold [CT]) was used for randomisation based on the commercial tumour samples in July 2015, via quantitative RT-PCR using a 100-ng RNA input. In July 2016, the delta CT cut-off was revised to 1.50 based on the results of the tumour biopsy samples of the first 33 patients enrolled in this study. The median delta CT value was chosen to determine the cut-off based on the commercial samples and data from the study patients.

3. Results

This study was conducted between December 31, 2015 (first patient enrolled) and February 21, 2018 (last patient follow-up), with the final analysis performed after study close (database lock March 23, 2018).

3.1. Patient disposition

Of the 125 patients screened, 87 enrolled and initiated treatment ($n = 44$ in the patritumab group and $n = 43$ in the placebo group) (Fig. 2). All 87 patients

discontinued study treatment. The primary reason for discontinuation was PD per RECIST version 1.1 (52.9%). Discontinuations because of TEAEs were higher in the patritumab versus placebo group (15.9% versus 4.7%). Overall, 44 patients (24/44 in the patritumab group and 20/43 in the placebo group) died during the study (defined as death occurring anytime during study treatment or survival follow-up periods), with six of those deaths (three each in the patritumab and placebo group) occurring while on treatment (defined as death occurring on or after the first dose date to 21 days after the last dose date of any study drug).

3.1.1. Patient demographics and baseline characteristics

In all, 87 patients (58.6% HRG high and 41.4% HRG low) were randomised and treated. Characteristics were similar between treatment groups (Table 1). The median (range) age was 59.0 (33–76) years. The majority of patients had tumour stage IV SCCHN (88.5%, $n = 77$), an ECOG performance status of 1 (51.7%, $n = 45$) and had prior treatment with radiation therapy (59.8%, $n = 52$). Tumour biopsies that were used to determine HRG RNA levels were primarily from archival (82.8%, $n = 72$ [HRG high: n = 43; HRG low: n = 29]) compared with fresh (17.2%, $n = 15$ [HRG high: n = 8; HRG low: n = 7]) specimens.

3.2. Treatment exposure

Mean (standard deviation) treatment duration was 24.2 (16.8) weeks for patritumab and 27.7 (23.3) weeks for placebo. Mean (standard deviation) treatment duration was similar between patritumab and placebo groups for cetuximab (22.4 [17.0] versus 27.0 [23.7] weeks), carboplatin (15.2 [4.9] versus 15.0 [6.9] weeks) and cisplatin (12.8 [7.2] versus 13.5 [7.4] weeks). Overall, a median of 6.5 (1–24) patritumab cycles were completed. In the patritumab group (n = 44), patients received a median

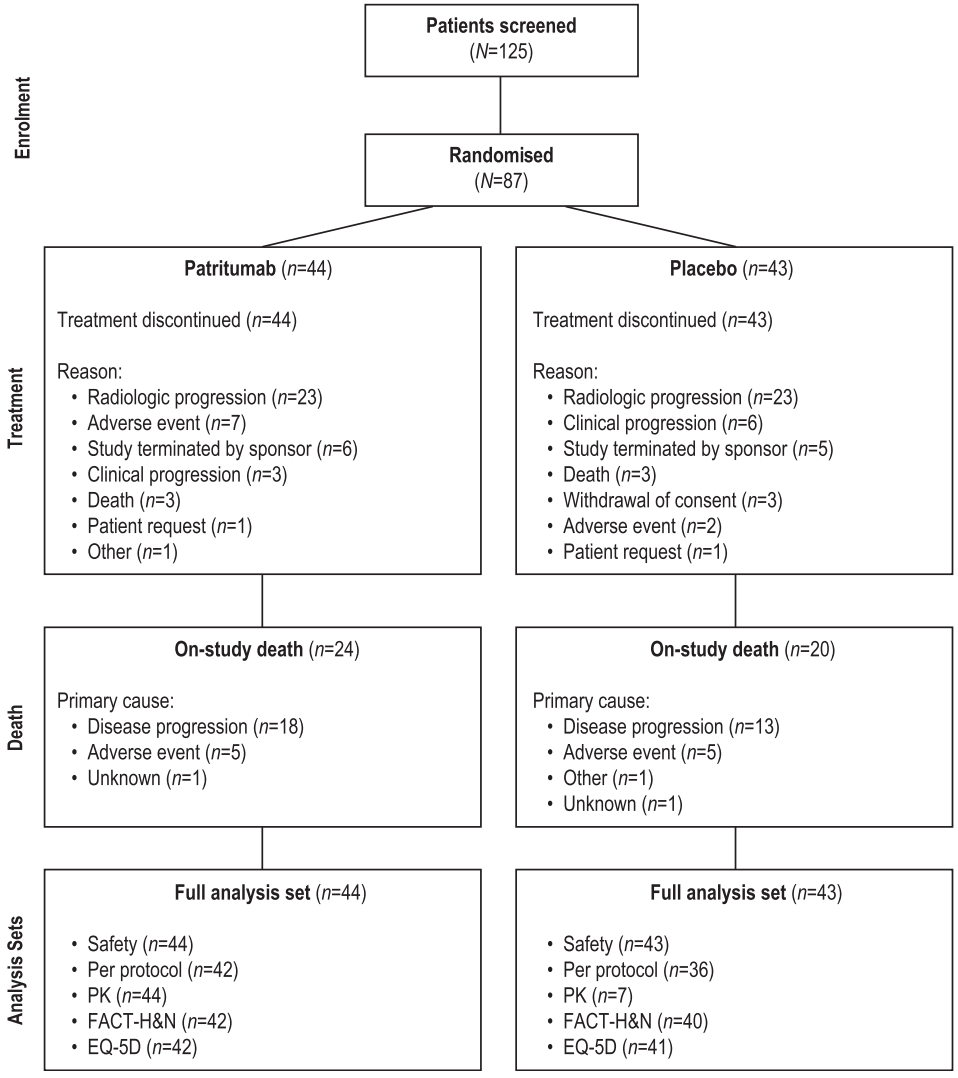

Fig. 2. Patient disposition. EQ-5D, EuroQoL Quality of Life Scale; FACT-H&N, Functional Assessment of Cancer Therapy—Head and Neck; PK, pharmacokinetics.

Table 1
Patient demographics.

Characteristics	Patritumab[a] (n = 44)	Placebo[b] (n = 43)	Total (N = 87)
Age, years, median (range)	58.5 (35–73)	62.0 (33–76)	59.0 (33–76)
≥65 years, n (%)	12 (27.3)	16 (37.2)	28 (32.2)
Sex, male, n (%)	36 (81.8)	36 (83.7)	72 (82.8)
Cancer type, n (%)			
Oral cavity	17 (38.6)	11 (25.6)	28 (32.2)
Oropharynx	8 (18.2)	14 (32.6)	22 (25.3)
Hypopharynx	9 (20.5)	9 (20.9)	18 (20.7)
Larynx	4 (9.1)	5 (11.6)	9 (10.3)
Other	6 (13.6)	4 (9.3)	10 (11.5)
Tumour stage at study entry, n (%)			
III	3 (6.8)	3 (7.0)	6 (6.9)
IV (A–C)	40 (90.9)	37 (86.1)	77 (88.5)
Other	1 (2.3)	3 (7.0)	4 (4.6)
Prior systemic cancer therapy, n (%)	14 (31.8)	16 (37.2)	30 (34.5)
Best response to prior therapy, n (%)			
CR	9 (20.5)	10 (23.3)	19 (21.8)
PR	2 (4.5)	2 (4.7)	4 (4.6)
SD	0	1 (2.3)	1 (1.1)
PD	1 (2.3)	2 (4.7)	3 (3.4)
Unknown	2 (4.5)	1 (2.3)	3 (3.4)
Prior radiation therapy, n (%)	25 (56.8)	27 (62.8)	52 (59.8)
Baseline ECOG performance status, n (%)			
0	19 (43.2)	22 (51.2)	41 (47.1)
1	25 (56.8)	20 (46.5)	45 (51.7)
2	0	1 (2.3)	1 (1.1)
HRG expression status, n (%)			
High	26 (59.1)	25 (58.1)	51 (58.6)
Low	18 (40.9)	18 (41.9)	36 (41.4)
HPV status, n (%)			
Positive	8 (18.2)	8 (18.6)	16 (18.4)
Negative	36 (81.8)	35 (81.4)	71 (81.6)
Smoking status, n (%)			
Current	14 (31.8)	17 (39.5)	31 (35.6)
Former	25 (56.8)	23 (53.5)	48 (55.2)
Never	4 (9.1)	3 (7.0)	7 (8.0)
Missing	1 (2.3)	0	1 (1.1)
Smoking duration, years,[c] median (range)	(n = 32) 32.5 (2–59)	(n = 36) 39.0 (6–55)	(n = 68) 35.9 (2–59)
Baseline 12-lead ECG, n (%)			
Normal	25 (56.8)	26 (60.5)	51 (58.6)
Abnormal (NCS)	19 (43.2)	16 (37.2)	35 (40.2)
Missing	0	1 (2.3)	1 (1.1)

CR, complete response; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; HPV, human papillomavirus; HRG, heregulin; NCS, not clinically significant; PD, progressive disease; PR, partial response; SCCHN, squamous cell carcinoma of the head and neck; SD, stable disease.

[a] Patritumab group = patritumab + cetuximab + cisplatin or carboplatin.

[b] Placebo group = placebo + cetuximab + cisplatin or carboplatin.

[c] Patients for whom data was available.

of 5.0 (2–6) carboplatin (n = 31) cycles or a median of or 5.0 (1–6) cisplatin (n = 15) cycles. In the placebo group (n = 43), patients received a median of 5.0 (1–6) cycles for both carboplatin (n = 35) or cisplatin (n = 9). Two patients in the patritumab group and one in the placebo group switched from cisplatin to carboplatin.

Mean (standard deviation) cumulative doses of patritumab and placebo received per patient were 73.4 (63.0) mg/kg and 84.7 (64.3) mg/kg and the mean (standard deviation) durations of treatment were 24.2 (16.8) weeks and 27.7 (23.3) weeks, respectively. Of the 44 patients treated with patritumab, 86.4%, 11.4% and 2.3% required 0, 1 or ≥2 patritumab dose reductions, respectively.

3.3. Efficacy

3.3.1. PFS and OS

Median PFS was 5.6 (95% CI, 4.1–6.5) months for the patritumab group and 5.5 (95% CI, 4.2–6.4) months for the placebo group (HR 0.99 [95% CI, 0.6–1.7]; P = 0.96) (Fig. 3A). In the HRG-high subgroup, median PFS was 5.6 (95% CI, 4.1–11.2) months for the patritumab group and 5.6 (95% CI, 3.1–8.3) months for the placebo group (HR 0.93 [95% CI, 0.5–1.8]; P = 0.82) (Fig. 3B). Similarly, no differences were observed between treatment groups in the HRG-low or HPV-negative subgroups (Fig. 3C–D). The sample size for the HPV-positive group (n = 8 each in the patritumab and placebo groups) was too small to offer meaningful interpretation.

There was no statistical difference in OS between treatment groups in the ITT population or in the HRG subgroup (Fig. 4A–C); median OS was non-evaluable in the HPV subgroups. For the ITT population, median OS was 10.0 months in the patritumab group and 12.7 months in the placebo group (HR 1.26 [95% CI, 0.69–2.29]; P = 0.46).

3.3.2. Tumour response

The ORR for all patients was 36.4% in the patritumab group and 27.9% in the placebo group (Supplementary Table S1). Response rates were similar between treatment groups, regardless of HRG or HPV status. Best (minimum) percent change in sum of diameters from baseline in target lesions per patient is illustrated in Fig. 5. The mean (standard deviation) best (minimum) percent change in sum of longest diameters (mm) from baseline in target lesion (mm) in the patritumab and placebo groups, respectively, were 32.2% (31.3%) and 19.1% (36.3%) in the ITT population and 32.0% (32.6%) and 22.5% (32.7%) in the HRG-high subgroup.

3.4. Safety

3.4.1. TEAEs and SAEs

All patients experienced at least one TEAE (Table 2). TEAEs grade ≥III were more frequent in the patritumab group than in the placebo group (84.1% versus 60.5%). The proportion of all patients with TEAEs grade ≥III was similar between the HRG-high (36/51, 70.6%) and HRG-low (27/36, 75.0%) groups. TEAEs considered related to patritumab/placebo were reported

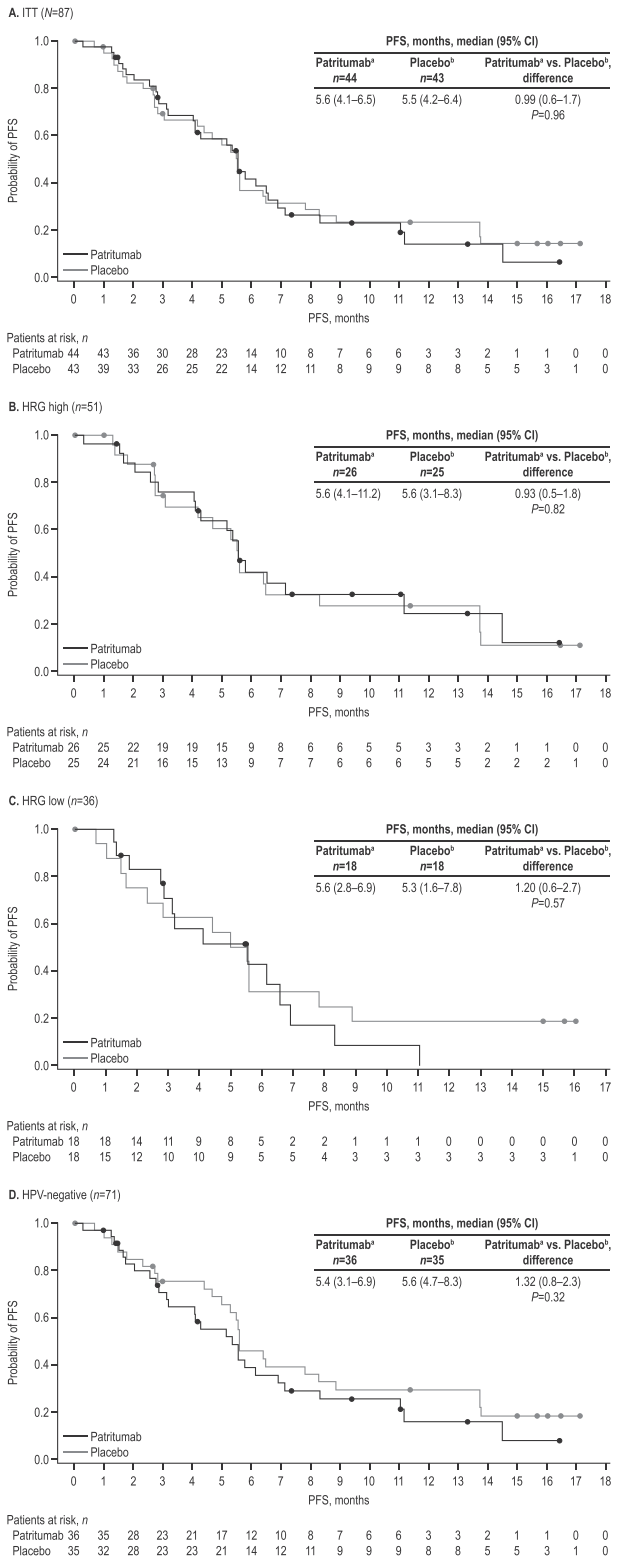

Fig. 3. Progression-free survival. **A,** ITT. **B,** HRG high. **C,** HRG low. **D,** HPV-negative. [a]Patritumab group = patritumab + cetuximab + cisplatin or carboplatin; [b]Placebo group = placebo + cetuximab + cisplatin or carboplatin. CI, confidence interval; HPV, human papillomavirus; HRG, heregulin; ITT, intent-to-treat; PFS, progression-free survival.

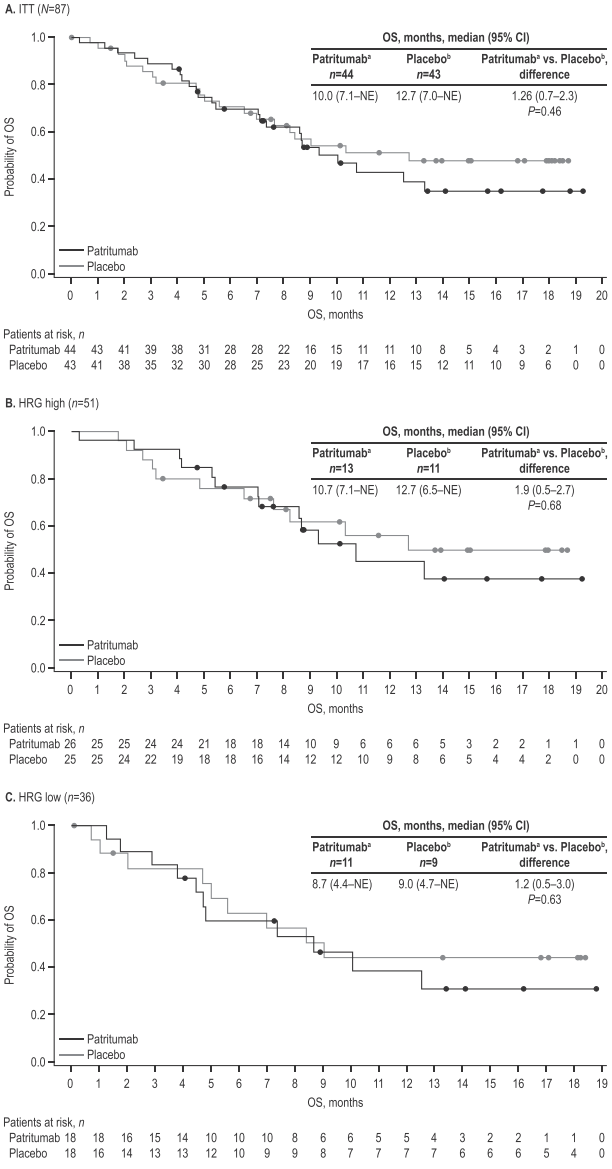

Fig. 4. Overall survival. **A,** ITT. **B,** HRG high. **C,** HRG low. HPV subgroups were non-evaluable for OS; median (95% CI) OS with patritumab versus placebo was: NE (4.1–NE) vs. 5.6 (2.7–8.2) in the HPV-positive subgroup and 9.3 (5.4–13.3) vs NE (9.0-NE) in the HPV-negative subgroup. [a]Patritumab group = patritumab + cetuximab + cisplatin or carboplatin; [b]Placebo group = placebo + cetuximab + cisplatin or carboplatin. CI, confidence interval; HPV, human papillomavirus; HRG, heregulin; ITT, intent-to-treat; NE, non-evaluable; OS, overall survival.

in 52.3% ($n = 23$) of patients in the patritumab group and 37.2% ($n = 16$) of patients in the placebo group. Grade ≥III TEAEs considered related to patritumab in the patritumab group were reported in 20.5% ($n = 9$) of patients and included rash (6.8%, $n = 3$), anaemia (4.5%, $n = 2$), neutropenia (4.5%, $n = 2$), acne (2.3%, $n = 1$), dermatitis acneiform (2.3%, $n = 1$), ejection fraction decreased (2.3%, $n = 1$), empyema (2.3%, $n = 1$), hypomagnesemia (2.3%, $n = 1$), melena (2.3%,

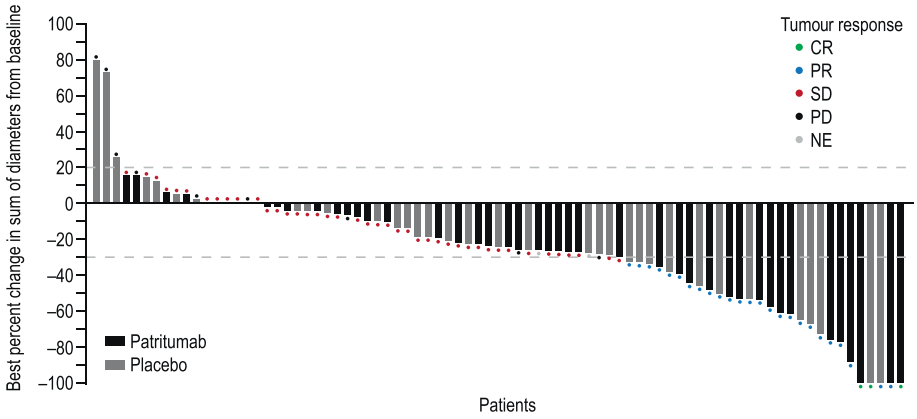

Fig. 5. Best (minimum) percent change in sum of diameters from baseline in target lesions. Dotted line represents response (−30) and disease progression (+20). CR, complete response; ITT, intent-to-treat; NE, non-evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

Table 2
Treatment-emergent adverse events.

TEAE	Number of patients with a TEAE, *n* (%)			
	Patritumab[a] (*n* = 44)		Placebo[b] (*n* = 43)	
	All grades	Grade ≥III	All grades	Grade ≥III
Any TEAE	44 (100)	37 (84.1)	43 (100)	26 (60.5)
TEAE, by preferred term				
Rash	20 (45.5)	6 (13.6)	21 (48.8)	0
Anaemia	18 (40.9)	5 (11.4)	12 (27.9)	6 (14.0)
Hypomagnesemia	16 (36.4)	2 (4.5)	15 (34.9)	1 (2.3)
Nausea	16 (36.4)	0	14 (32.6)	2 (4.7)
Acneiform dermatitis	15 (34.1)	6 (13.6)	8 (18.6)	3 (7.0)
Paronychia	15 (34.1)	3 (6.8)	4 (9.3)	0
Neutropenia	13 (29.5)	5 (11.4)	11 (25.6)	4 (9.3)
Diarrhoea	12 (27.3)	0	6 (14.0)	1 (2.3)
Hypokalaemia	12 (27.3)	3 (6.8)	2 (4.7)	0
Weight decreased	12 (27.3)	0	10 (23.3)	0
Decreased appetite	11 (25.0)	1 (2.3)	11 (25.6)	3 (7.0)
Fatigue	11 (25.0)	0	7 (16.3)	1 (2.3)
Thrombocytopaenia	10 (22.7)	0	14 (32.6)	4 (9.3)
Asthenia	9 (20.5)	0	11 (25.6)	3 (7.0)
Dysphagia	9 (20.5)	5 (11.4)	4 (9.3)	1 (2.3)
Vomiting	9 (20.5)	0	7 (16.3)	0
Mucosal inflammation	8 (18.2)	1 (2.3)	2 (4.7)	0
Dyspnoea	7 (15.9)	4 (9.1)	5 (11.6)	1 (2.3)
Skin fissures	7 (15.9)	1 (2.3)	6 (14.0)	0
Conjunctivitis	6 (13.6)	0	4 (9.3)	0
Constipation	6 (13.6)	0	4 (9.3)	0
Dry skin	6 (13.6)	1 (2.3)	7 (16.3)	0
Cough	5 (11.4)	0	5 (11.6)	0
Leucocytosis	5 (11.4)	0	0	0
Stomatitis	5 (11.4)	1 (2.3)	3 (7.0)	0
Headache	3 (6.8)	0	5 (11.6)	1 (2.3)
Folliculitis	2 (4.5)	0	5 (11.6)	0
Hypophosphataemia	2 (4.5)	0	5 (11.6)	4 (9.3)

TEAE, treatment emergent adverse event.
[a] Patritumab group = patritumab + cetuximab + cisplatin or carboplatin.
[b] Placebo group = placebo + cetuximab + cisplatin or carboplatin.

n = 1), palmar-plantar erythrodysesthesia syndrome (2.3%, *n* = 1), rash pustular (2.3%, *n* = 1) and stomatitis (2.3%, *n* = 1).

SAEs were reported in 43.2% and 37.2% of patients in the patritumab and placebo groups, respectively (Table 3 and Supplementary Table S2). The proportion

Table 3
SAEs in ≥2 patients.

SAE	Number of patients with an SAE, *n* (%)			
	Patritumab[a] (*n* = 44)		Placebo[b] (*n* = 43)	
	All grades	Grade ≥III	All grades	Grade ≥III
Any treatment emergent SAE	19 (43.2)	19 (43.2)	16 (37.2)	14 (32.6)
Treatment emergent SAE, by preferred term (in ≥2 patients)				
Dehydration	3 (6.8)	2 (4.5)	2 (4.7)	2 (4.7)
Pneumonia	4 (9.1)	3 (6.8)	0	0
Tumour haemorrhage	0	0	4 (9.3)	3 (7.0)
Device-related infection	2 (4.5)	2 (4.5)	0	0
Sepsis	0	0	2 (4.7)	1 (2.3)
Cardiovascular insufficiency	1 (2.3)	1 (2.3)	1 (2.3)	1 (2.3)

SAE, serious adverse event.
[a] Patritumab group = patritumab + cetuximab + cisplatin or carboplatin.
[b] Placebo group = placebo + cetuximab + cisplatin or carboplatin.

of all patients with SAEs grade ≥III was 29.4% (15/51) in the HRG-high and 50.0% (18/36) in the HRG-low group. SAEs were considered related to patritumab in 6.8% (*n* = 3) of patients in the patritumab group and 7.0% (*n* = 3) in the placebo group. Patritumab dose reduction was reported in six (13.6%) patients, considered related to patritumab in four (9.1%) patients. Treatment-emergent SAEs leading to death occurred in five (11.4%) patients in the patritumab group and seven (16.3%) patients in the placebo group. In the patritumab group, one (2.3%) death due to cardiovascular insufficiency was considered related to cetuximab. In the placebo group, one (2.3%) death due to hypoxia was considered related to patritumab/placebo by the investigator, but the investigator was blinded to the treatment group. No other deaths were considered related to treatment.

3.4.2. Development of HAHAs

In all, five patients (*n* = 3 HRG high and *n* = 2 HRG low) had ≥1 HAHA-positive titre over the course of the study. One patient had a transient positive titre (1:40) which was negative at study end, and four patients had a positive titre. Of the four patients with a positive titre at study end, two had a 1:<10 titre, one had a 1:20 titre and one had a 1:80 titre.

3.5. Pharmacokinetics

The PK analysis set included 11 patients in the patritumab group and seven patients in the placebo group. At 7 h post-infusion, mean (standard deviation) patritumab concentration was 318.5 (85.7) μg/mL, decreasing to 242.6 (65.0) μg/mL, 183.2 (88.9) μg/mL, 91.2 (39.8) μg/mL and 43.5 (18.5) μg/mL at 24, 48, 168 and 336 h post-infusion, respectively; by 504 h, patritumab concentration had decreased to 54.0 (83.7) μg/mL (Supplementary Fig. S1A).

In the patritumab group, mean (standard deviation) cetuximab concentration was 169.3 (57.5) μg/mL at the end of the first infusion, increasing to 196.5 (42.1) μg/mL at 4 h post-infusion and then decreasing to 127.7 (24.1) μg/mL, 95.7 (35.8) μg/mL and 34.9 (13.0) μg/mL at 24, 48 and 168 h post-infusion, respectively (Supplementary Fig. S1B). In the placebo group, mean (standard deviation) cetuximab concentration was 117.7 (48.1) μg/mL at the end of the first infusion, increasing to 167.4 (80.4) μg/mL at 4 h post-infusion and then decreasing to 109.0 (47.3) μg/mL, 81.0 (40.0) μg/mL and 35.1 (21.0) μg/mL at 24, 48 and 168 h post-infusion, respectively (Supplementary Fig. S1B).

3.6. Patient-reported outcomes

3.6.1. FACT H&N

Mean (standard deviation) FACT H&N total scores, which measure overall QoL for patients with head and neck cancers, at baseline were similar between the patritumab (97.0 [23.4]) group and the placebo (100 [25.4]) group. At day 1 cycle 15, the LS mean difference from baseline was similar between the patritumab (−2.1 [95% CI, −13.5, 9.2]) and placebo (−1.8 [95% CI, −12.0, 8.5]) groups (LS mean difference: −0.4 [95% CI, −15.7, 15.0] (Supplementary Table S3). Similar results were reported for the following subscales: functional well-being, which assessed patient-perceived ability to function successfully in daily life (LS mean difference: −0.7 [95% CI, −4.4, 4.2]), emotional well-being, which assessed patients' level of anxiety and fear surrounding their illness (LS mean difference: −1.1 [95% CI, −4.5, 2.3]), social well-being, which assessed patient satisfaction with the support they receive from friends and family (LS mean difference: −0.2; 95% CI, −3.9, 3.5) and physical well-being, which assessed patient satisfaction with their energy level and mobility (LS mean difference: −1.1 [95% CI, −5.1, 2.9]).

3.6.2. EQ-5D-5L

The mean (standard deviation) of EQ-5D-5L (measuring patient satisfaction with mobility, self-care, usual activities, pain/discomfort and anxiety/depression) scores at baseline were similar between patritumab (0.7

[0.2] and placebo (0.7 [0.2]) groups and remained stable at the last observation for both patritumab (0.7 [0.3]) and placebo (0.7 [0.3]) groups. For EQ VAS, mean (standard deviation) VAS score at baseline was 67.4 (21.4) in the patritumab group and 72.1 (15.1) in the placebo group. At last observation on treatment, mean (standard deviation) VAS score decreased, indicating a perceived decrease in overall health, to 64.1 (19.6) in the patritumab group and 69.4 (16.3) in the placebo group.

4. Discussion

Data from this phase II, randomised, placebo-controlled study showed that patritumab, cetuximab and platinum were not superior to cetuximab and platinum therapy for the treatment of R/M SCCHN. Current NCCN guidelines recommend cetuximab as treatment for R/M SCCHN [5]. In a phase III study of 117 patients with R/M SCCHN, the addition of cetuximab to cisplatin treatment showed increased clinical activity compared with cisplatin alone, though no differences in PFS or OS were observed [19]. Further, cetuximab response is limited; up to 36% of patients respond to the EXTREME regimen and 13% of patients respond to cetuximab monotherapy [6,20]. Many patients who initially respond develop resistance, which may be because of an overexpression of HRG [6,21]. High *HRG* expression has also been shown to correlate with reduced PFS and OS in SCCHN [10,11]. As this phase Ib study demonstrated activity of patritumab plus cetuximab with platinum-based therapy in patients with R/M SCCHN [17], the clinical relevance of HRG as a biomarker in SCCHN was evaluated in this study.

In the current study, compared with cetuximab plus platinum therapy, combination treatment with patritumab did not improve PFS or OS in the ITT population or in the HRG-high subgroup. *HRG* expression, therefore, does not appear to be a useful predictive biomarker of benefit from patritumab. Interestingly, patients who were HPV-positive had slightly but not significantly, better OS (non-evaluable versus 5.6 months) and PFS (6.5 versus 2.7 months) results in the patritumab group compared with the placebo group, though the number of patients in this subgroup were too small to detect a clinically meaningful difference.

Overall, treatment with patritumab in combination with cetuximab and cisplatin or carboplatin in the current study was tolerable. Patritumab-related TEAEs were reported in 52.3% of patients in the patritumab group. Notably, patritumab-related TEAEs were also reported in 37.2% of patients in the placebo group, though misattribution of TEAEs is not uncommon. A study investigating 398 patients across two phase III trials found that approximately 50% of TEAEs reported in the placebo groups were attributed to the study drug [22]. TEAEs grade ≥III were more frequently reported in the patritumab versus the placebo group (84.1% versus 60.5%). However, the proportion of patients reporting SAEs were similar between groups (43.2% versus 37.2%). Six patients had a dose reduction, four of which were because of a patritumab-related TEAE. Interestingly, a higher proportion of patients in the HRG-low subgroup had TEAEs grade ≥III compared with the HRG-high subgroup (50.0% versus 29.4%). The PK profiles in this study were similar to those reported in the phase I study of patritumab + cetuximab + platinum chemotherapy [17]. In both the placebo and patritumab groups, cetuximab concentration increased in the first 6 h post-dosing before steadily declining, indicating that patritumab had a minimal effect on cetuximab PK. Patient QoL was assessed using both the FACT-H&N and EQ-5D-5L. Results showed that showed that QoL remained stable over the course of the study and was similar for both the patritumab and placebo groups.

While the cetuximab + platinum chemotherapy has been the standard of care of R/M SCCHN, the treatment landscape is changing. The phase III KEYNOTE-048 study found that first-line treatment with pembrolizumab, a PD-L1 inhibitor, improved OS compared with the EXTREME regimen in patients with R/M SCCHN whose tumours expressed PD-L1 with a combined positive score ≥20 (14.9 months versus 10.7 months; $P = 0.0007$) and combined positive score ≥1 (12.3 months versus 10.3 months, $P = 0.0086$) [23]. Combination treatment with pembrolizumab and chemotherapy also improved OS compared with the EXTREME regimen in the overall patient population (13.0 months versus 10.7 months; $P = 0.0034$). In the current study, though patritumab did not improve OS with cetuximab and platinum therapy, patritumab was tolerable. Given these data, it is hypothesised that the resistance mechanism for cetuximab in SCCHN may not only be driven by HER3, but also by other not-yet-defined pathways (e.g. tyrosine kinase receptors and other cellular receptors) that may be mediating resistance. U3-1402, a first-in-class HER3-targeting antidrug conjugate composed of patritumab covalently conjugated to a drug-linker (MAAA-1162a) containing a drug component (MAAA-1181a), is currently in phase I/II trials for the treatment of HER3-expressing breast cancer (clinicaltrials.gov identifier: NCT02980341) [24].

4.1. Limitations

A low number of patients in subgroups may have limited the ability to assess efficacy in HRG and HPV subgroups. In the majority of patients, archived tumour tissue was used to determine HRG status, and there may exist some temporal heterogeneity in HRG levels. As paired analysis from fresh and archived tumour tissue was not done, it cannot be ruled out that patients with

HRG-high status—as ascertained from *archival* tumour biopsies—may in fact be of HRG-low status from *fresh* tumour biopsies (and vice versa). However, to the knowledge of the authors, no published literature in SCCHN demonstrates that HRG levels change over time. Further, there was good representation of HRG-high and HRG-low status in both archived and fresh tumour tissue in the current study.

5. Conclusions

The combination of patritumab with cetuximab and platinum therapy was tolerable but was not more efficacious compared with cetuximab and platinum therapy. This study will not continue into a phase III clinical trial.

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Conflicts of interest statement

M.F. reports receiving research grants from AstraZeneca, Boehringer Ingelheim, Merck and MSD, has received consultancy and advisory honoraria from Achilles, AstraZeneca, Bristol-Myers Squibb, Celgene, Eli-Lilly, Merck, MSD, Novartis, Pfizer, Pharmamar and Roche. J.G. is an employee and stockholder of Daiichi Sankyo. K.J.H. reports receiving speakers' bureau honoraria from AstraZeneca, Bristol-Myers Squibb, Merck-Serono, MSD and Pfizer, is a consultant/advisory board member for Amgen, AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Merck-Serono, MSD and Pfizer, reports receiving commercial research grants from AstraZeneca and reports receiving commercial research support from AstraZeneca, Boehringer-Ingelheim and MSD. No potential conflicts of interest were disclosed by the other authors.

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Appendix A. Supplementary data

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