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Protocol for the EACH trial: a multicentre phase II study evaluating the safety and antitumour activity of the combination of avelumab, an anti-PD-L1 agent, and cetuximab, as any line treatment for patients with recurrent/metastatic head and neck squamous cell cancer (HNSCC) in the UK

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ABSTRACT

Introduction Head and neck cancer is the eighth most common cancer in the UK. Current standard of care treatment for patients with recurrent/metastatic squamous cell head and neck carcinoma (HNSCC) is platinum-based chemotherapy combined with the anti-epidermal growth factor receptor (anti-EGFR) monoclonal antibody, cetuximab. However, most patients will have poor median overall survival (OS) of 6–9 months despite treatment. HNSCC tumours exhibit an immune landscape poised to respond to immunotherapeutic approaches, with most tumours expressing the immunosuppressive receptor programmed death-ligand 1 (PD-L1). We undertook the current study to determine the safety and efficacy of avelumab, a monoclonal antibody targeting the interaction between PD-L1 and its receptor on cytotoxic T-cells, in combination with cetuximab.

Methods and analysis This is a multi-centre, single-arm dose de-escalation phase II safety and efficacy study of avelumab combined with cetuximab; the study was to progress to a randomised phase II trial, however, the study will now complete after the safety run-in component. Up to 16 participants with histologically/cytologically recurrent/metastatic squamous cell carcinoma (including HNSCC) who have not received cetuximab previously will be recruited. All patients will receive 10 mg/kg avelumab and cetuximab (500, 400 or 300 mg/m^2 depending on the cohort open at time of registration) on days 1 and 15 of 4-week cycles for up to 1 year, (avelumab not given cycle 1 day 1). A modified continual reassessment method will be used to determine dose de-escalation. The primary objective is to establish the safety of the combination and to determine the optimum dose of cetuximab. Secondary objectives include assessing evidence of antitumour activity by evaluating response rates and disease control rates at 6 and 12 months as well as progression-free and OS.

Ethics and dissemination Approval granted by City and East REC (18/LO/0021). Findings will be published in peer-reviewed journals and disseminated at conferences.

Trial registration number NCT03494322.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Study design with sequenced drug starts offers the opportunity for translational work to better understand the biology underpinning any activity seen.
⇒ Study design provides extensive follow-up and multiple objective measures assessing the safety and efficacy of the combination treatment.
⇒ The revised study design is non-randomised and unblinded with small patient numbers.
⇒ Frequent clinical obligations may result in failure of retention of subjects.

INTRODUCTION

Head and neck cancer is the eighth most common cancer in the UK, with approximately 12 200 new cases every year.[1] The vast majority of head and neck cancers are squamous cell carcinomas (HNSCC) accounting for more than 90% of the cancers located in the upper aerodigestive tract.[2 3] Despite aggressive treatment of early stage disease, approximately 50% of patients will develop recurrent disease, with a poor median overall survival (OS) of 6–9 months. The majority of these patients will be unsuitable for local salvage treatments, and treatment is usually

aimed instead at improving symptoms and extending life expectancy.[4 5]

Cisplatin and 5-fluorouracil (CF) was the accepted first line treatment for platinum naïve patients for decades. The addition of the anti-EGFR monoclonal antibody, cetuximab, to platinum based duplet chemotherapy was established following the randomised EXTREME trial.[6] In this study, median OS was 10.1 months in the cetuximab arm versus 7.4 months with chemotherapy alone (p=0.04). Patients with platinum-resistant disease have limited second line treatment options in the form of taxane-based chemotherapy or single agent immunotherapy, both with low response rates and modest survival benefit.

Immune checkpoint inhibitors have been explored with encouraging results across multiple solid tumours including HNSCC. Anti-programmed cell death protein 1 (anti-PD-1) monoclonal antibodies like nivolumab and pembrolizumab have been approved in the USA and Europe for treatment in the platinum-failure setting for recurrent/metastatic HNSCC patients.[7 8] As evidenced by results of KEYNOTE-048, the field is now focused on earlier stages of disease, and how to optimally combine and sequence existing immunotherapies.[9] The FDA and Europe have approved pembrolizumab with CF chemotherapy for all patients and as a single agent for patients whose tumours express programmed death-ligand 1 (PD-L1) Combined Predictive Score ≥1.

Chemotherapy is associated with several treatment-related toxicities and may not be suitable for patients with a poor performance status. Cetuximab monotherapy has been studied in HNSCC, demonstrating response rates of 10%–13% with a median OS of 5.2–6.1 months.[10] As a monoclonal IgG1 antibody targeted towards EGFR, which is overexpressed in >90% of HNSCC, cetuximab prevents dimerisation and inhibits subsequent activation of tyrosine kinase-mediated signalling pathways. Importantly, it also initiates natural killer (NK) cell antibody-dependent cell-mediated toxicity (ADCC) by triggering the NK cell Fc receptor, CD16.[10 11] As such, cetuximab can elicit antitumour activity as a monotherapy or in combination with chemotherapy.

While nivolumab and pembrolizumab have shown encouraging results in HNSCC, further improvements are required. These human or humanised monoclonal antibodies targeting the PD-1/PD-L1 axis are either IgG4 isotypes, which do not mediate ADCC responses, or IgG1 isotypes which have been specifically engineered to eliminate ADCC activity. Avelumab, in contrast, is a fully human IgG1 anti-PD-L1 monoclonal antibody which also has potential ADCC properties.[12] It is currently approved in the USA and Europe for the treatment of Merkel Cell Carcinoma[13] and has also shown efficacy in advanced renal cell carcinoma.[14] We hypothesise that the antitumour activity from avelumab encompasses not only interruption of the PD-1/PD-L1 axis but also by enhancing activation of the ADCC pathway and augmentation of the NK response. The latter of these mechanisms will be assisted by the secondary actions of cetuximab, in addition to its direct inhibition of the frequently overexpressed EGFR in HNSCC tumours.

METHODS AND ANALYSIS

Trial blinding

This is an open-label trial; therefore, the sponsor, investigator and subject will know the treatment administered.

Study design

This is a multi-centre phase II safety and efficacy study of combination avelumab and cetuximab therapy for subjects, 18 years or older, with pathologically documented recurrent or metastatic squamous cell carcinoma (including HNSCC) who have not previously received cetuximab. This study is a single arm dose de-escalation design which will recruit up to 16 patients with squamous cell carcinoma. Subjects will be enrolled to a single treatment group of varying doses of cetuximab, depending on the cohort open at the time of enrolment. A modified continual reassessment method (mCRM) will be used

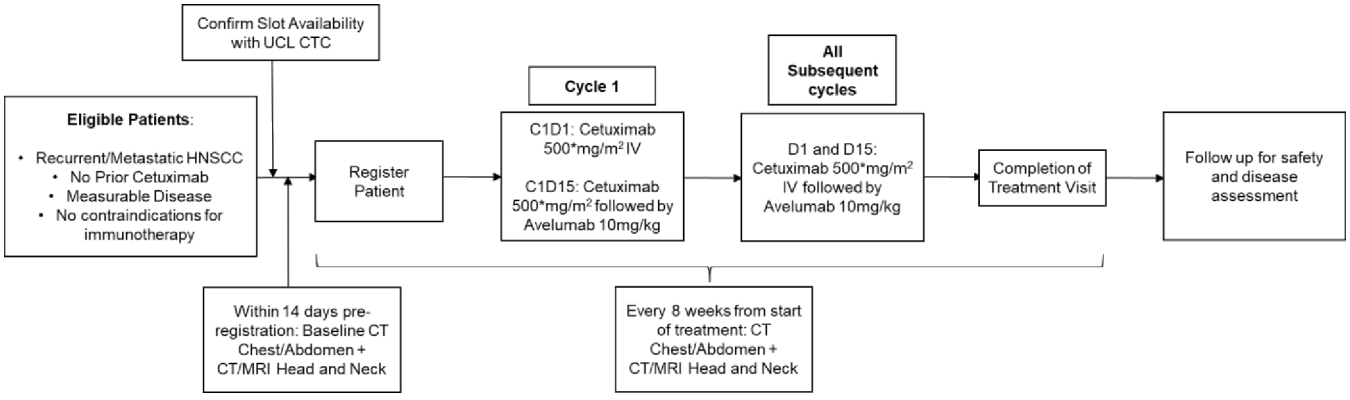

Figure 1 Trial design for phase II study of avelumab and cetuximab for patients with recurrent/metastatic head and neck squamous cell carcinoma (HNSCC). *Cetuximab dose depends on cohort at time of registration. UCL CTC, Cancer Trials Centre, University College London.

Box 1 Main subject inclusion criteria

Histologically or cytologically confirmed recurrent or metastatic squamous cell carcinoma of any site that is considered incurable by local therapies.
No previous treatment with cetuximab for metastatic/recurrent disease or anti-PD-1, anti-PD-L1 or anti-PD-L2 agent.
Age ≥18 years.
WHO Performance Status 0 or 1.
Measurable disease according to RECIST version 1.1.
Adequate bone marrow function.
Adequate liver function.
Adequate renal function.
Adequate venous access for administration of treatment and collection of blood samples for exploratory biological samples.
Life expectancy of >3 months.
Women of child-bearingchildbearing potential and male patients with partners of child-bearingchildbearing potential must agree to use highly effective contraception methods from date of informed consent, which must be continued for up to 6 months after last treatment administration.
Able to give informed consent.
Willing and able to comply with the protocol for the duration of the study, including the treatment plan, investigations required and follow upfollow-up visits.
PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

Box 2 Main subject exclusion criteria

Patients with sino-nasal cancers.
Disease suitable for treatment with curative intent.
Treatment with any investigational agents within 4 weeks prior to the first dose of trial treatment.
Anticancer monoclonal antibody therapy within 4 weeks prior to registration.
Chemotherapy, targeted small molecule therapy or radiotherapy within 2 weeks prior to registration.
Persistent grade ≥2 toxicity related to prior therapy (except alopecia, grade 2 sensory neuropathy).
Concurrent or previous malignancy that could compromise assessment of the primary or secondary endpoints of the trial.
Women who are pregnant or breast feeding.
Grade 3 or 4 peripheral neuropathy.
Any serious and/or unstable pre-existing medical, psychiatric or other condition, or laboratory abnormalities that may increase the risk associated with study participation or treatment.
Patients who are not able to give informed consent for any reason.
Active central nervous system (CNS) metastases and/or carcinomatous meningitis.
Hepatitis B or C infection at screening.
Known history of testing positive for HIV or known AIDS.
Prior organ transplantation including allogenic stem-cell transplantation.
Have a history of (non-infectious) pneumonitis that required steroids, or current pneumonitis.
Active infection requiring systemic therapy.
Has received a live vaccine within 28 days prior to first dose of trial treatment.
Immunodeficiency/receiving systemic steroid or immunosuppressive therapy.
Active autoimmune disease that might deteriorate when receiving immune-checkpoint inhibitor.
Current use of immunosuppressive medication.
Significant cardiovascular disease.

to determine dose de-escalation. Figure 1 is a schematic illustrating the trial design.

Trial schedule

The trial schedule (online supplemental table 1) summarises the trial procedures to be performed at each visit. It may be necessary to perform these procedures at unscheduled timepoints at the discretion of the investigator, depending on clinical need. Furthermore, additional evaluations and testing may be deemed necessary by the sponsor for reasons related to subject safety.

Patient selection

Subjects who meet the required inclusion and exclusion criteria as shown in boxes 1 and 2 are eligible for enrolment into the study (see online supplemental table 2 for full subject inclusion criteria and online supplemental table 3 for exclusion criteria).

Avelumab and cetuximab: trial treatment dosage, formulation and frequency

Avelumab is a fully human anti-PD-L1 IgG1 monoclonal antibody. The drug product is a sterile, clear and colourless concentrate for solution provided at a concentration of 20 mg/mL in type I glass vials closed with a rubber stopper and sealed with an aluminium flip off crimp seal closure. Cetuximab is a chimeric monoclonal IgG1 antibody produced in a mammalian cell line (Sp2/0) by recombinant DNA technology. It is supplied as a 5 mg/mL colourless solution for infusion. Cetuximab is supplied for the trial as 20 mL of solution in a vial (type I glass) with a stopper and an aluminium/polypropylene seal. Both products must be stored in a refrigerator (2°C–8°C).

This study will recruit up to 16 patients using a dose de-escalation design as follows:

- Patients will be recruited in cohorts of three.
- Each cycle is 28 days and dosing will continue until progression, unacceptable toxicity or for a maximum of 12 months.
- All patients will receive the same dose of avelumab (10 mg/kg) starting on day 15 of cycle 1, and thereafter given on days 1 and 15 of each cycle.
- Cetuximab will be given on days 1 and 15 of each cycle. The starting dose of cetuximab will depend on the dose level under study at the time the patient is registered. The first dose of cetuximab to be studied will be 500 mg/m2.
- Depending on the number of patients experiencing dose limiting toxicity (DLT) during the first 6 weeks after starting treatment in each cohort, a decision will be made either to expand the cohort or to de-escalate to the next cohort (400mg/m^2, then to 300 mg/m^2 if further DLTs are seen).

The dosing calculations for avelumab and cetuximab combination doses should be based on the body weight. Body surface area for cetuximab should be calculated according to local policy. If the subject's weight on the day of treatment administration differs by >10% from the weight used to calculate the dose, the dose must be recalculated.

Prior to the first infusion of cetuximab, patients must receive premedication with an antihistamine and a corticosteroid at least an hour prior to the administration of the drug. This premedication is also recommended for all subsequent infusions. Avelumab should always be administered after cetuximab when they are given together, with a 60 min break in between the two drugs. Following avelumab infusions, patients must be observed for 30 min postinfusion for potential infusion reactions.

Trial objectives

The primary objective is to establish the safety of the combination of avelumab and cetuximab and to determine the optimum dose of cetuximab to use in this combination in patients with recurrent or metastatic SCC. The secondary objectives are to assess antitumour activity, tolerability of the trial treatments and the safety of allowing cetuximab pre-medication steroid doses down to 2 mg. The primary endpoint is the occurrence of DLT. The secondary endpoints are objective response (iCR or iPR) at 6 or 12 months using iRECIST,[15] disease control at 6 and 12 months using iRECIST, duration of response using iRECIST, best overall response using iRECIST, time to progression, progression free survival, OS, frequency and severity of adverse events (AEs) and treatment related dose delays or treatment discontinuation.

Adverse events

The investigator or qualified designated personnel will assess each subject to evaluate for potential new or worsening AEs as specified in the detailed trial schedule and more frequently if clinically indicated. AEs will be graded and recorded throughout the study in accordance to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. Toxicities will be characterised in the context of toxicity grading, causality and action taken with regard to trial treatment. AEs will be recorded from the time the subject signs the consent through 90 days.

The full trial protocol details include detailed descriptions and management of infusion-related AEs, skin AEs, gastrointestinal AEs, pulmonary AEs, hepatic AEs, renal AEs, electrolyte disturbances, immune-related myocarditis, thyroid AEs, adrenal insufficiency, type 1 diabetes, hypophysitis and ophthalmological AEs. The investigators acknowledge that the AEs listed in the protocol are not exhaustive, and any AE which may be immune-related should be evaluated to determine if is caused by the drugs administered.

The study protocol dictates the parameters for determination of patient safety and for trial suspension and discontinuation. Importantly, the dose of avelumab should not be reduced; it can only be withheld or permanently discontinued. Cetuximab may be withheld, permanently discontinued, or continued at a reduced dose, according to the instructions in the original protocol. If avelumab is discontinued, then cetuximab must also be discontinued. However, if cetuximab is discontinued, avelumab monotherapy can continue if allowed by the protocol.

Determination of dose-limiting toxicity of cetuximab

Depending on the number of patients experiencing DLT during the first 6 weeks after starting treatment in each cohort, a decision will be made either to expand the cohort or to de-escalate to the next cohort. A DLT is defined as any grade 3 or 4 adverse reaction requiring a dose reduction in cetuximab, or any adverse reaction requiring a more than 14 day treatment delay for either drug.

Sample size calculation

Up to 16 patients will be enrolled. This is a dose de-escalation study, using a mCRM design. The aim is to identify the maximum tolerated dose (MTD) of cetuximab when combined with avelumab. The MTD is the highest dose combination of avelumab plus cetuximab that has an estimated risk of causing DLT equal to or closest to 33% (the target toxicity level). An empiric power model is assumed for the dose–toxicity relationship, with a normal prior distribution (mean=0, variance=1.34) for the model parameter. We assume the 500 mg/m^2 cetuximab dose has an expected DLT risk equal to 33% and calculate the prior probabilities of DLT for the 300 mg/m^2 and 400 mg/m^2 cetuximab doses to be 15% and 23%, respectively, using the approach of Lee and Cheung.[16] The first three patients will be treated at the highest dose of avelumab plus cetuximab combination. If no DLTs are observed in these three patients, a further three patients will receive the same dose combination. If no DLTs are observed in these first six patients, the estimated probability that a patient receiving the highest dose combination experiencing a DLT will be less than 10%. These six patients will be followed up for a minimum of 8 weeks to ensure late-onset toxicities are not dose-limiting. If any of these patients experiences a DLT, either in the first or second cohort of three patients, estimates of the probability of DLT will be calculated using the available data and the next three patients will receive the cetuximab dose with a probability of DLT less than but closest to 33%. At the end of the trial, the dose with an estimated DLT probability less than but closest to 33% will be taken forwards for any future clinical studies.

Analysis of the secondary endpoints—including objective response at 6 and 12 months, as well as disease control at 12 months will be evaluated according to iRECIST criteria. Time to progression and survival data will be calculated from the date of registration to the event of concern. Duration of response will be calculated from the date of first response assessment showing partial/complete response to the date of the response assessment documenting disease progression according to iRECIST.

Biological samples and exploratory endpoints

Collection of archival tumour tissue is mandatory for all patients. All tumour samples available from previous biopsies will be analysed in parallel with new biopsies to appreciate the changes in the immune landscape over time. Tumour biopsies are optional for patients, but where possible, they will be collected at the timepoints specified in assessment schedule shown in box 1. Whenever consent is obtained, this should allow tissue and blood samples to be collected at baseline, on cycle 1 day 15, prior to cycle three and on progression. In the case of blood samples, up to 60 mL blood will be collected for analysis of ctDNA (8–10 mL), exosomes (16–20 mL) and immunological evaluation (24–30 mL).

Tissue samples will be fixed in formalin and embedded into paraffin blocks (FFPE). FFPE samples will undergo a series of analyses including multiplex immunohistochemistry to provide a geographical assessment of the immune landscape, evaluating the distribution and spatial relationships between tumour-infiltrating cellular subsets. Whole exome sequencing, gene expression profiling and exosome profiling will be conducted to explore the relationship between mutational load and inflammatory/predictive signatures and response to avelumab. Multi-parametric analysis of fresh core biopsies and peripheral blood mononuclear cells at baseline, 'on therapy' and on progression will be performed with optimised staining panels for flow cytometry (13 parameters) and CyTOF (40 parameters). Based on immunophenotyping data obtained from responding and non-responding patients, functional immunological assays will be carried out in a subset of patients to determine humoral or cellular responses.

Patient and public involvement

A patient representative was involved in the design and conduct of the study, and is a member of the Trial Management Group. Results of the study will be disseminated to the study participants on request.

ETHICS AND DISSEMINATION

The investigator and sponsor of the study will adhere to all the relevant guidance, laws and statutes applicable to the performance of clinical trials. The trial will be conducted in accordance with the World Medical Association Declaration of Helsinki, 'Ethical Principles for Medical Research involving Human Research' (1996 version) and in accordance with the terms and conditions of the ethical approval given to the trial by the City and East Research Ethics Committee (ref: 18/LO/0021) and Health Research Authority in the UK. A clinical trial authorisation has been granted for the trial.

Findings from the study will be published in peer-reviewed journals and disseminated at national and international conferences.

Patient identifiable data, including initials and date of birth will be collected by UCL CTC. UCL CTC will preserve patient confidentiality and will not disclose or reproduce any information by which patients could be identified. Data will be stored in a secure manner and UCL CTC trials are registered in accordance with the Data Protection Act 2018 and GDPR, with the Data Protection Officer at UCL.

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Contributors KN and MF wrote the clinical protocol. MF, RM, JS, AK provided clinical input and are members of the Trial Management Group. GW provided statistical advice on the protocol and specifically on the mCRM. SF, RB, LW were responsible for collating comments on the protocol and for submitting the protocol (and amendments) to the regulatory authorities. JW provided nursing input. LE, HL, VS, JH provided advice on the translational research aspects of the protocol. ELD provided PPI input.

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Competing interests MDF has received an institutional research grant and honoraria for consultancy from Merck.All other authors declare no conflicts of interest.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

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Supplementary Material

Table 1 Trial schedule for phase II study of avelumab in combination with cetuximab for patients with recurrent or metastatic SCC.

Assessment	**Pre-Registration[a]**	**Cycle 1**		**Cycle 2**		**Every 8 weeks[h]**	**Cycle 3 and subsequent cycles**		**After last treatment**		
		Day 1[f]	**Day 15[g]**	**Day 1[g]**	**Day 15[g]**		**Day 1[g]**	**Day 15[g]**	**Completion of treatment[i]**	**F/U to PD**	**F/U after PD**
Histological/cytological confirmation of HNSCC[b]	**X**										
CT/MRI imaging + RECIST reporting[c]	**X**					**X**				**X[j]**	
Hepatitis B&C testing if required[c]	**X**										
Medical History	**X**										
Cancer signs + symptoms	**X**										
Smoking status	**X**										
Concomitant medication	**X**	**X**	**X**	**X**	**X**		**X**	**X**	**X**		
Adverse events	**X**	**X**	**X**	**X**	**X**		**X**	**X**	**X**	**X[k]**	**X[k]**
Physical Examination (**F**ull or **T**argeted)	**F**	**T**	**T**	**T**	**T**		**T**		**F**		
Weight	**X**		**X**	**X**	**X**		**X**	**X**	**X**		
Vital Signs (pulse, BP, RR, T)	**X**		**X**	**X**	**X**		**X**	**X**	**X**		
WHO Performance Status	**X**	**X**	**X**	**X**	**X**		**X**	**X**	**X**		
Haematology[d]	**H1**	**H2**	**H2**	**H2**	**H2**		**H2**	**H2**	**H2**		
Biochemistry[e]	**B1**	**B2**	**B2**	**B2**	**B2**		**B3/B2[n]**	**B2**	**B3**		
Calculated CrCl	**X**	**X**	**X**	**X**	**X**		**X**	**X**	**X**		
Pregnancy test (in WOCBP)	**X**	**X**		**X**			**X**				
P16 IHC (oropharyngeal only)	**X**										
Review patient diary			**X**	**X**	**X**		**X**	**X**	**X**	**X[k]**	
Tumour biopsy[p]		**X[o]**	**X**				**X[q]**				**X[l]**
Blood for circulating biomarkers[p]		**X[o]**	**X**	**X**			**X[q]**		**X**		**X[l]**
Collection of archival tissue[o]		**X**									
Survival Status											**X[m]**

LEGEND: RECIST – Response evaluation criteria in solid tumours; CT – Computerised Tomography; MRI – Magnetic Resonance Imaging; IHC – immunohistochemistry; WOCBP – women of child bearing potential, CrCl – creatinine clearance, PD – progressive disease, BP – blood pressure, RR – respiratory rate, T - temperature

a. Within 14 days prior to registration unless otherwise specified.

b. Time before registration not specified

c. Within 28 days prior to registration

d. H1=FBC + differential, PT, APTT. H2 = FBC + differential

e. B1 = serum urea, creatinine, sodium, potassium, calcium, magnesium, total protein, albumin, total bilirubin, AST and/or ALT, Alkaline phosphatase, LDH, CRP, amylase, glucose, free T4, TSH, random cortisol. B2 = serum urea, creatinine, sodium, potassium, calcium, magnesium, total protein, albumin, total bilirubin, AST and/or ALT, Alkaline phosphatase, LDH. B3 =serum urea, creatinine, sodium, potassium, calcium, magnesium, total protein, albumin, total bilirubin, AST and/or ALT, alkaline phosphatase, LDH, free T4, TSH, random cortisol

f. Within 7 days prior to cycle 1 day 1 (do not need to be repeated if they were done pre-registration and were within 7 days prior to 1st day of treatment)

g. Within 3 days prior to treatment day

h. +/- one week

i. 28-35 days after last trial treatment administration

j. Every 3 months to end of year 2

k. Every 28 days (+/- 7 days) for up to 90 days after last treatment administration

l. At progression of disease (PD) only – biopsy optional for all patients at PD

m. Every 6 months to end of year 2

n. Alternating cycles. If clinically indicated amylase, glucose

o. Within 14 days prior to cycle 1 day 1

p. Optional

q. Within 10 days prior to cycle 3 day 1 only

Table 2. Full subject inclusion criteria

1.	Histologically or cytologically confirmed recurrent or metastatic squamous cell carcinoma of any site that is considered incurable by local therapies
2.	No previous treatment with cetuximab for metastatic/recurrent disease or anti-PD-1, anti-PD-L1 or anti-PD-L2 agent.
3.	Age ≥ 18 years
4.	World Health Organisation Performance Status 0 or 1
5.	Measurable disease according to RECIST v 1.1
6.	Adequate bone marrow function: • Absolute neutrophils ≥ 1.5 x 10^9/L • Platelets ≥ 100 x 10^9/L • Haemoglobin ≥ 90g/L (may have been transfused)
7.	Adequate liver function: • Total bilirubin ≤ 1.5x ULN (≤ 3x ULN for patients with Gilbert's syndrome) • AST or ALT ≤ 2.5x ULN (≤ 5x ULN for patients with liver metastases). NB: if both AST and ALT are performed, both results must meet the eligibility criteria
8.	Adequate renal function • Estimated creatinine clearance ≥ 30mL/min estimated using validated creatinine clearance calculation (e.g. Cockcroft-Gault or Wright formula)
9.	Adequate venous access for administration of treatment and collection of blood samples for exploratory biological samples.
10.	Life expectancy of >3 months
11.	Women of child-bearing potential and male patients with partners of child-bearing potential must agree to use highly effective contraception methods from date of informed consent, which must be continued for up to 6 months after last treatment administration
12.	Able to give informed consent, indicating that the patient has been informed of and understands the experimental nature of the study, possible risks and benefits, trial procedures and alternative options.
13.	Willing and able to comply with the protocol for the duration of the study, including the treatment plan, investigations required and follow up visits.

Table 3. Full subject exclusion criteria

1.	Patients with sino-nasal cancers.
2.	Disease suitable for treatment with curative intent.
3.	Treatment with any investigational agents within 4 weeks prior to the first dose of trial treatment.
4.	Anti-cancer monoclonal antibody therapy within 4 weeks prior to registration.
5.	Chemotherapy, targeted small molecule therapy, or radiotherapy within 2 weeks prior to registration.
6.	Persistent grade ≥ 2 toxicity related to prior therapy, except the following: • Alopecia • Sensory neuropathy grade 2 • Other grade 2 toxicity as long as it does not constitute a safety risk based on the investigator's judgement.
7.	Patients with concurrent or previous malignancy that could compromise assessment of the primary or secondary endpoints of the trial.
8.	Women who are pregnant or breast feeding. Women of child-bearing potential must have a negative pregnancy test to confirm they are not pregnant.
9.	Grade 3 or 4 peripheral neuropathy.
10.	Any serious and/or unstable pre-existing medical, psychiatric or other condition, or laboratory abnormalities that may increase the risk associated with study participation or study treatment administration or may interfere with the interpretation of study results and, in the judgement of the investigator, would make the patient inappropriate for entry into this study.
11.	Patients who are not able to give informed consent for any reason.
12.	Active central nervous system (CNS) metastases and/or carcinomatous meningitis; subjects with previously treated brain metastases may participate provided they: • Are stable, without evidence of progression for at least four weeks prior to the first dose of trial treatment • Have no evidence of new or enlarging brain metastases • Have no evidence of leptomeningeal disease • Are not using steroids for at least 7 days prior to trial treatment
13.	Hepatitis infection at screening: • Hepatitis B virus (HBV) (i.e. positive HBV surface antigen) • Hepatitis C virus (HCV) (i.e. HCV RNA if anti-HCV antibody screening test positive)
14.	Known history of testing positive for HIV or known acquired immunodeficiency syndrome. Testing for HIV is not mandatory, however if this test has been done the result should be known prior to registration.
15.	Prior organ transplantation including allogenic stem-cell transplantation.
16.	Have a history of (non-infectious) pneumonitis that required steroids, or current pneumonitis.

17.	Active infection requiring systemic therapy.
18.	Has received a live vaccine within 28 days prior to first dose of trial treatment (seasonal flu vaccines that do not contain live virus are permitted).
19.	Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment (N.B: the use of physiologic doses of corticosteroids may be approved after consultation with UCL Cancer Trials Centre).
20.	Active autoimmune disease that might deteriorate when receiving an immune-checkpoint inhibitor. Patients with the following are eligible: • Autoimmune-related hyperthyroidism or autoimmune-related hypothyroidism who are in remission or on a stable dose of thyroid-replacement hormone • Vitiligo • Psoriasis.
21.	Current use of immunosuppressive medication, except for the following: • Intranasal, inhaled, topical steroids, or local steroid injection (eg intra-articular injection) • Systemic corticosteroids at physiologic doses ≤ 10mg/day of prednisolone or equivalent • Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication).
22.	History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organising pneumonia (i.e., bronchiolitis obliterans, cryptogenic organising pneumonia), or evidence of active pneumonitis on screening chest CT scan (History of radiation pneumonitis in the radiation field is permitted).
23.	Significant cardiovascular disease: • Cerebrovascular accident or stroke within 6 months prior to registration • Myocardial infarction within 6 months prior to enrolment • New York Heart Association cardiac disease (class II or greater) • Serious cardiac arrhythmia requiring medication • Unstable angina.
24.	Known prior severe hypersensitivity to either investigational product or any component in their formulations, including known severe hypersensitivity reactions to monoclonal antibodies (CTCAE v5 Grade ≥ 3).
25.	Other severe acute or chronic medical conditions including immune colitis, inflammatory bowel disease, immune pneumonitis, pulmonary fibrosis.
26.	Patients with a history of keratitis, ulcerative keratitis or severe dry eyes.