

Poster # 424b**Patritumab or Placebo Plus Cetuximab and Platinum-Based Therapy in Squamous Cell Carcinoma of the Head and Neck (SCCHN): a Phase 2 Study**

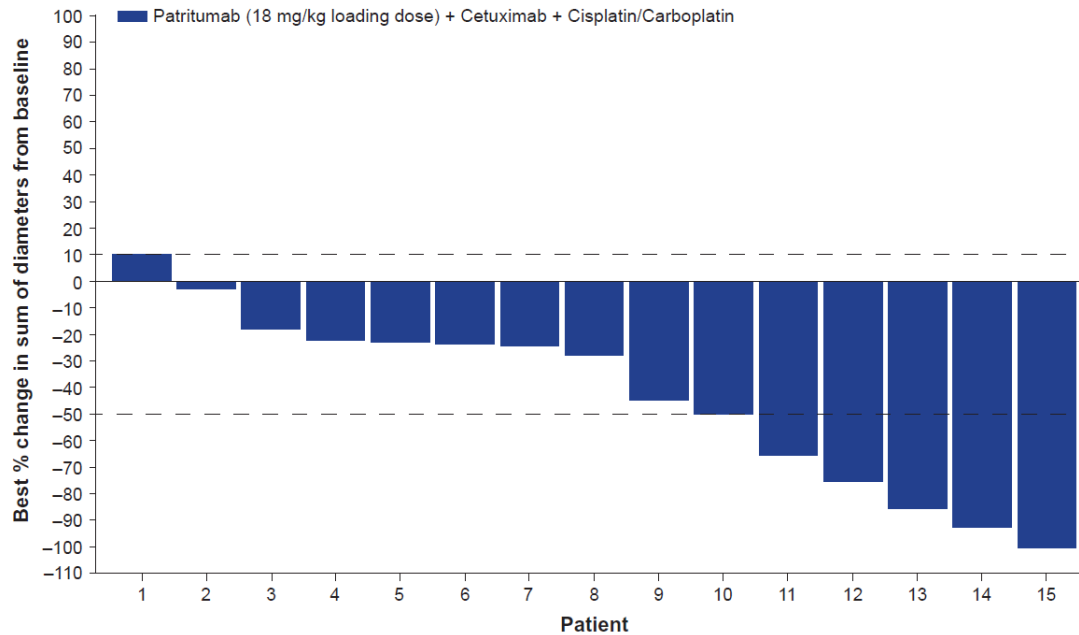
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INTRODUCTION

- Patritumab is a fully human anti-epidermal growth factor receptor 3 (HER3) monoclonal antibody that binds to the extracellular domain of HER3¹⁻³
 - HER3 signaling is associated with high expression of heregulin (HRG)⁴, which has been shown to be important for tumour growth and proliferation
 - When combined with epidermal growth factor receptor (EGFR) inhibitors, patritumab enhances in vitro anti-tumour activity and prevents HER3 activation following anti-EGFR treatment^{1,3,5}
- Evidence is growing that HRG presence affects disease progression and survival
 - In a phase 2 study in non-small-cell lung cancer, treatment with patritumab + erlotinib increased progression-free survival (PFS) in patients with high HRG mRNA expression (HRG-high)^{6,7}
- A phase 1b study in patients with SCCHN (clinicaltrials.gov identifier: NCT02350712) demonstrated safety, tolerability, and tumour response of patritumab + cetuximab + cisplatin or carboplatin and informed the patritumab dose regimen in the phase 2 study
 - As of January, 2016, the tumour response rate (complete response [CR] + partial response [PR]) for all 15 patients was 47%: CR: n=3 (20%); PR: n=4 (27%); stable disease (SD): n=8 (53%), and progressive disease (PD): n=0 (0%) (disease control rate = 100%)
 - The best (minimum) percent change in the sum of diameters from baseline in target lesions for each patient is illustrated in **Figure 1**⁹
 - The recommended phase 2 dose of patritumab is 18-mg/kg loading dose, followed by a 9-mg/kg maintenance dose every 3 weeks, maintaining patritumab trough concentrations above the inhibitory concentration 90% derived from preclinical data⁸

Figure 1. Best (minimum) percent change in sum of diameters from baseline in target lesions (safety analysis population)⁹



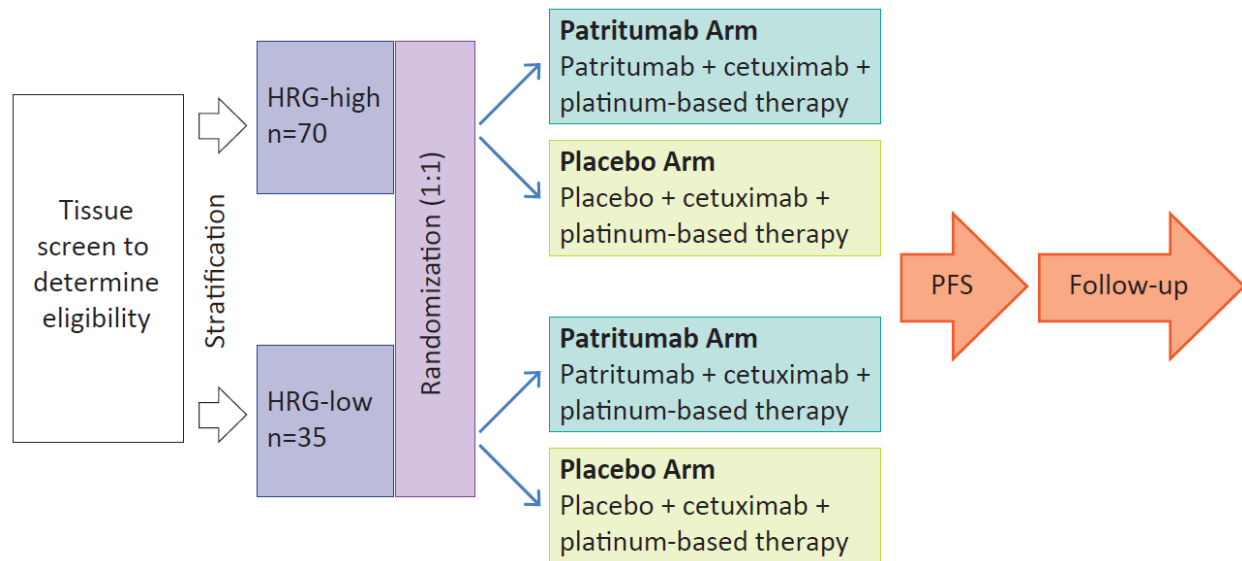
PURPOSE

- A phase 2 study was designed to evaluate the safety, efficacy, and pharmacokinetics (PK) of first-line patritumab + cetuximab + platinum vs. placebo + cetuximab + platinum in heregulin HRG-expressing recurrent and/or metastatic SCCHN (NCT02633800)
- The design of the phase 2 study is presented

STUDY DESIGN

Overall Design

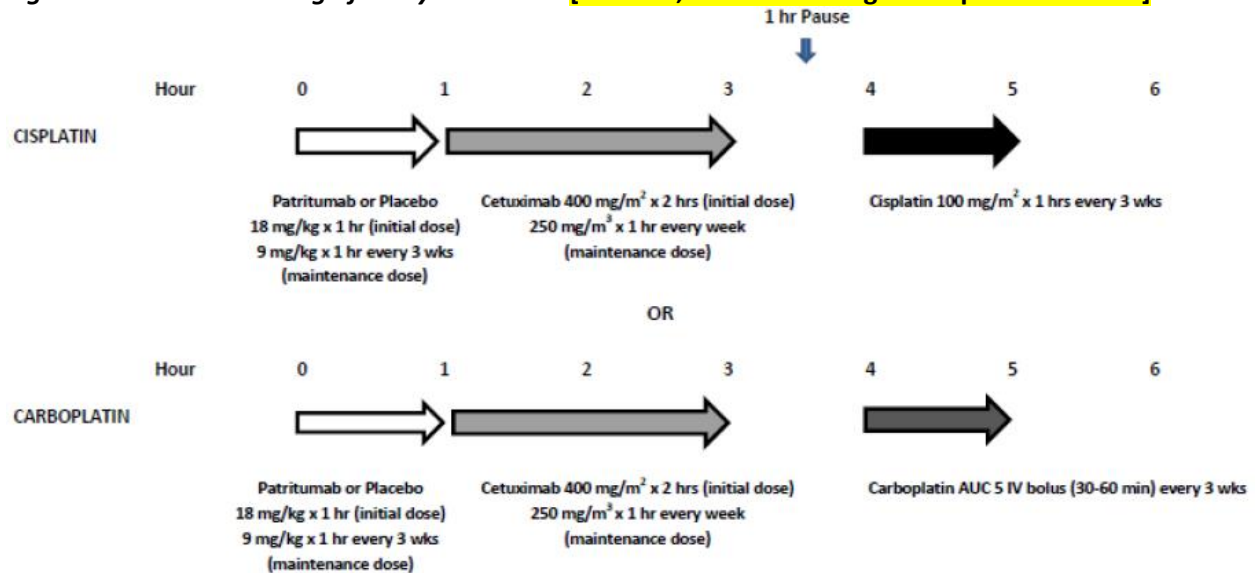
- This is a multicentre, randomised, placebo-controlled, double-blind phase 2 study in Europe to evaluate PFS and safety in recurrent/metastatic first-line SCCHN in subjects treated with either patritumab or placebo + cetuximab + platinum-based therapy (**Figure 2**)
- Approximately 105 subjects from ~35 sites in Europe will be stratified 2:1 by HRG status (70 HRG-high; 35 with low HRG expression [HRG-low]), and then randomized 1:1 to the patritumab or placebo arm

Figure 2. Phase 2 study design

HRG, heregulin; PFS, progression-free survival.

Treatment

- Study treatment regimens, shown in **Figure 3**, include:
 - Intravenous patritumab (18-mg/kg loading dose; 9-mg/kg maintenance dose every 3 weeks [q3w]) or placebo
 - Cetuximab (400-mg/m² loading dose; 250-mg/m² maintenance dose weekly)
 - Up to 6 cycles of cisplatin (100 mg/m² q3w) or carboplatin (area under the curve of 5)
- Patients demonstrating CR, PR, or SD will be treated with patritumab or placebo + cetuximab + ≤6 cycles platinum for the study duration (until all patients have died or ≥13 months postrandomisation of last patient)
 - Those benefiting may continue therapy with patritumab + cetuximab (platinum-based therapy for ≤6 cycles) uninterrupted in an open-label extension phase until progressive disease, toxicity, or withdrawal
- Reasons for discontinuation include: PD per Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 or clinician's assessment, adverse event (AE), death, withdrawal of consent, significant protocol violation, or study termination by the study

Figure 3. Order and timing of study treatment [Authors, we will omit figure if space is needed]

AUC, area under the curve; hr, hour; IV, intravenous; wk, week.

Study End Points

- Primary efficacy end point: PFS
- Secondary end points
 - *Efficacy*: overall survival (OS); overall response rate (ORR [CR + PR])
 - *PK*: area under the curve from 0-t and maximum concentration for serum patritumab, cetuximab, and platinum
 - *Safety*: treatment-emergent AEs, grade ≥ 3 AEs; myocardial infarction status; electrocardiograms, vital signs, physical exams, and including human anti-human antibody incidence

Key Inclusion Criteria

- Age ≥ 18 years
- Histologically confirmed recurrent disease or metastatic SCCHN
- Documented HRG expression (per archived or fresh biopsy)
- Measurable disease per RECIST criteria
- Human papilloma virus (HPV) status or p16 (HPV surrogate)
- Eastern Cooperative Oncology Group performance status 0 or 1
- Adequate haematological, renal, and hepatic function
- Prothrombin time or partial thromboplastin time ≤ 1.5 x upper limit of normal

Key Exclusion Criteria

- Left ventricular ejection fraction <50%
- Prior EGFR targeted regimen or anti-HER3 therapy
- Prior treatment with chemotherapy for recurrent/metastatic disease; anti-cancer therapy between biopsy and submission of sample; platinum-containing drug therapy with radiotherapy <6 months prior to the study; or therapeutic or palliative radiation therapy or major surgery ≤4 weeks prior to the study
- Squamous cell tumours of the nasopharynx
- Known history of brain metastases or active brain metastases
- History of other malignancies, except adequately treated non-melanoma skin cancer, curatively treated in-situ disease, or other solid tumours curatively treated with no evidence of disease for ≥2 years
- Presence of hemorrhagic tumors (for patients receiving carboplatin)
- Uncontrolled hypertension, clinically significant electrocardiograph findings, myocardial infarction ≤1 year prior to enrolment; symptomatic congestive heart failure, unstable angina, or arrhythmia requiring medication

Assessments

- A schedule of key study assessments is shown in **Table 1**
- At tissue screening (prior to study screen), patients provided informed consent for tumour tissue and were screened for serious AEs related to the biopsy procedure
- At study screen, criteria for study inclusion (including HRG level HPV) will be assessed

Table 1. Schedule of Assessments

Assessment	Screening (≤14 days)	Treatment Cycle	Every 6 Weeks	End of Study	
				21 Days After Last Dose	40 Days After Last Dose
ECOG	X	<ul style="list-style-type: none"> • Cycle 1: Day 1 predose; Day 8; Day 15 • Cycles 2, 3, and ≥4: Day 1 		X	
ECHO or MUGA	X	<ul style="list-style-type: none"> • Cycle 3 and every 3rd subsequent cycle: Day 1^a 		X	
ECG (12-lead)	X			X	
AEs	X	<ul style="list-style-type: none"> • Cycle 1: Day 1 predose and EOI; Days 8 and 15 • Cycles 2, 3, and ≥4: Day 1^b 		X	X ^c
PK (all patients)		<ul style="list-style-type: none"> • Cycle 1: Day 1 predose^d and EOI • Cycles 2 and 3: Day 1 		X	
PK (subgroup; n=30)		<ul style="list-style-type: none"> • Cycle 1: Day 1 predose^d and EOI; Days 2, 3, 8, and 15 • Cycles 2 and 3: Day 1^e 			
HAHA		<ul style="list-style-type: none"> • Cycle 1: Day 1 predose^d • Cycles 2 and 3: Day 1 		X	
Tumour response ^f	X		X ^g	X	
Survival follow-up					X ^h
Biomarkers		<ul style="list-style-type: none"> • Cycle 1: Day 1 predoseⁱ • Cycles 2 and 3: Day 1 • End of Cycle 6 and every 4 cycles 		X	X

^aAdditional tests may be performed at the discretion of the investigator. The same test (echocardiogram [ECHO] or multigated acquisition scan [MUGA]) must be used for a subject throughout the study;

^bCan be collected on Days 8 and 15 in all subsequent cycles at the discretion of the Investigator;

^cForty days after last dose of study drug, adverse events (AEs) will be assessed via a phone call to the patient;

^dAssessment can be performed ≤3 days prior to visit;

^eCorresponds to Cycle 1, Day 21 (504 hours);

^fPer Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1;

^gEvery 6 weeks to Week 24 (±3 days), then every 12 weeks (±7 days) thereafter;

^hAfter discontinuation, survival status will be obtained (by phone) every 3 months for ≥13 months

ⁱBlood sample collected for cfDNA predose Cycle 1 Day 1, predose Cycle 2 Day 1, end of cycle 6, predose every 4 cycles, at progression (end of study treatment), and 40 days after last dose of study drug administered. Blood samples collected for exosome at

predose cycle 1 Day 1, predose cycle 2 Day 1, and dnd of cycle 6.

ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EOI, end of infusion; HAHA, human anti-human antibodies; PK, pharmacokinetics.

STATISTICAL DESIGN AND ANALYSIS

- Primary PFS analysis will be conducted when 53 PFS events are observed from approximately 70 patients with HRG-high status, providing 80% power to detect a 79% increase in median PFS (hazard ratio [HR] of 0.56) in HRG-high subjects
 - A stratified log-rank test will be performed to compare the treatment groups for PFS and a stratified Cox proportional hazards model will be used to calculate median PFS and confidence intervals (CI)
- Under 2:1 (HRG high vs. low) stratification, approximately 105 subjects (70 HRG-high and 35 HRG-low) will be randomized in both strata to observe at least 75 PFS events, providing 81% power to detect a HR of 0.56 in PFS assuming 1-sided alpha of 0.05
- Differences in the ORR and OS between 2 arms in both the HRG-high and HRG-low population will be presented along with 2-sided 80% and 95% CIs based on the Wilson's score method with continuity correction
- Serum patritumab, cetuximab, and platinum concentrations and PK parameters will be summarised using descriptive statistics

STUDY STATUS

- Recruitment commenced December, 2015
- As of April 14, 2016, 6 subjects have enrolled among 4 investigational sites in Europe (**Figure 4**)
[Authors, these numbers can be updated prior to printing]_[KF1]

Figure 4. Location of enrolment sites [Authors, figure can be omitted if space is needed].



SUMMARY

- Data from the phase 1b study demonstrated safety, tolerability, and tumour response of patritumab + cetuximab + cisplatin or carboplatin and informed the patritumab dose regimen used in the phase 2 study
- The phase 2 study will evaluate PFS in patients with HRG-high status from subjects treated with patritumab or placebo + cetuximab + cisplatin or carboplatin, and further the confirm safety and tolerability of the combination of those agents
- Enrolment is open; additional study information is available on ClinicalTrials.gov (NCT02633800)

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