



A phase Ib/II study of HER3-targeting lumretuzumab in combination with carboplatin and paclitaxel as first-line treatment in patients with advanced or metastatic squamous non-small cell lung cancer

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ABSTRACT

Purpose This study investigated the safety and clinical activity of lumretuzumab, a humanised antihuman epidermal growth factor receptor 3 (HER3) monoclonal antibody, in combination with carboplatin and paclitaxel in first-line treatment of patients with squamous non-small cell lung cancer (sqNSCLC). HER3 ligand heregulin and HER3 protein expression were evaluated as potential biomarkers of clinical activity.

Patients and methods This open-label, phase Ib/II study enrolled patients receiving lumretuzumab at 800 mg (flat) in combination with carboplatin (area under the curve (AUC) 6 mg/mL×min) and paclitaxel (200 mg/m²) administered intravenously on a every 3-week schedule. Adverse event (AE) rates and tumour responses were determined. Heregulin messenger RNA (mRNA) and HER3 protein expression were investigated in archival tumour biopsies.

Results Altogether, 12 patients received lumretuzumab in combination with carboplatin and paclitaxel. The most frequent AEs were gastrointestinal, haematological and nervous system toxicities, which were generally mild and manageable. Partial responses were observed in 3 of 12 patients lasting 81, 177 and 207 days. All responses were achieved in tumours expressing higher heregulin mRNA levels.

Conclusion Lumretuzumab in combination with carboplatin and paclitaxel was well tolerated. Objective responses were enriched in tumours expressing higher heregulin mRNA levels.

INTRODUCTION

Lung cancer is one of the most frequent types of cancer worldwide both in terms of cases (2.1 million cases, 11.6% of total) and deaths (1.8 million deaths, 18.4%).¹ Among lung cancer subtypes, non-small cell lung cancer (NSCLC) is the most prevalent and about

Key questions

What is already known about this subject?

- ▶ Human epidermal growth factor receptor 3 (HER3) is associated with tumour development and poor clinical prognosis in different cancers.
- ▶ HER3 ligand heregulin may serve as a response prediction marker for HER3-targeting therapy.
- ▶ Heregulin expression levels are higher and more frequent in squamous non-small cell lung cancer (sqNSCLC).

What does this study add?

- ▶ HER3-targeting lumretuzumab in combination with carboplatin and paclitaxel was well tolerated.
- ▶ High heregulin expression levels enriched for patients more likely to show a clinical response.
- ▶ Clinically meaningful contribution to efficacy by lumretuzumab could not be demonstrated as compared with chemotherapy and immunotherapy.

How might this impact on clinical practice?

- ▶ HER3-targeting therapy may not add meaningful clinical benefit as to what has been shown for platinum-containing treatment regimens in the first-line treatment setting of sqNSCLC.

30% of NSCLC are squamous (sqNSCLC) cell carcinomas. Approximately 80% of lung cancer cases are diagnosed at stages III and IV.²

Until the advent of cancer immunotherapy, that is, checkpoint inhibition, platinum-based combination chemotherapy was the standard of care in patients with newly diagnosed advanced/metastatic sqNSCLC.³ Targeted agents such as epidermal growth

factor receptor (EGFR) inhibitors and anaplastic lymphoma kinase (ALK) inhibitors have shown clinical efficacy in molecular subgroups such as EGFR-mutant and ALK-rearranged NSCLC particularly of the non-squamous subtype⁴⁻⁶ but less so for all-comers treated with cetuximab, cisplatin and vinorelbine⁷ or for patients with sqNSCLC treated with necitumumab, gemcitabine and cisplatin.⁸ In the meantime, phase III studies have established antiprogrammed cell-death protein 1 (ligand) (PD-(L)1) compounds as the new standard of care in both sqNSCLC and non-squamous NSCLC. Pembrolizumab monotherapy has been approved as first-line therapy for patients with high PD-L1 expression ($\geq 50\%$)⁹ and for non-squamous histology in combination with platinum and pemetrexed¹⁰ and also for squamous histology in combination with carboplatin together with paclitaxel or nab-paclitaxel¹¹ independently of PD-L1 expression.

HER3 is a key dimerisation partner of HER family members which activates several signal transduction pathways, particularly the phosphoinositide-3-kinase (PI3K)/Akt pathway and is associated with tumour development and poor clinical prognosis in different cancers.¹² Lumretuzumab is a humanised, glycoengineered immunoglobulin G1 antibody which binds with high affinity and specificity to the extracellular domain of HER3. Prevention of the ligand heregulin binding to HER3 by lumretuzumab resulted in almost complete inhibition of HER3 heterodimerisation and phosphorylation as well as inhibition of tumour growth in cell-line-based mouse models.¹³ In a phase I study, the safety of lumretuzumab in patients with advanced solid tumours was evaluated; no dose-limiting toxicity was observed at doses up to 2000 mg every 2 weeks and the maximum tolerated dose was not reached. Lumretuzumab doses from 200 mg led to downregulation of membranous HER3 and a target-independent pharmacokinetic profile was observed from 400 mg doses and above.¹⁴

HER3 is widely expressed in NSCLC including sqNSCLC.¹⁵⁻¹⁶ In addition, higher expression levels of heregulin, the ligand of HER3, were associated with improved antitumour efficacy in preclinical models.¹⁷⁻¹⁹ Internal data from tumour bank samples as well as published data²⁰ provided evidence that heregulin expression levels are higher and more frequent in sqNSCLC as compared with NSCLC adenocarcinoma. Hence, we hypothesised that deprivation of HER3/PI3K-mediated cell survival signals by HER3-targeting lumretuzumab might provide improved treatment benefit especially in patients with sqNSCLC. At the time of study initiation, carboplatin and paclitaxel were considered a standard of care with an objective response rate of $\sim 25\%$.²¹ Therefore, carboplatin and paclitaxel were included as backbone chemotherapy regimen for the treatment of advanced/metastatic sqNSCLC.

METHODS

Study design

The study reported here was a phase Ib/II, open-label, non-randomised, multicentre study (ClinicalTrials.gov Identifier: NCT02204345) of lumretuzumab in combination with paclitaxel and carboplatin in patients with metastatic or advanced sqNSCLC. The primary objectives of the study were to evaluate the safety and tolerability of lumretuzumab in combination with carboplatin and paclitaxel and to estimate the efficacy of the combination, as measured by the objective response rate (ORR, defined as complete response (CR) rate+partial response (PR) rate).

As previously shown, pharmacokinetics of lumretuzumab was linear from ≥ 400 mg per patient, indicative of saturated target-mediated drug disposition, and maximum pharmacodynamic activity was reached in monotherapy ≥ 400 mg¹⁴. Therefore, a dose of 800 mg was defined as a fixed dose of lumretuzumab in this study.

Ethics

All patients provided written informed consent. The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki in five centres in Spain, Canada and Denmark.

Patients

Patients had a histologically confirmed diagnosis of advanced or metastatic (stage IIIb or IV²²) sqNSCLC. Patients had not received prior chemotherapy or targeted therapy for NSCLC. Eligible patients were ≥ 18 years of age, had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1 and had adequate haematology, blood chemistry and renal and liver function. Prior radiotherapy to control local symptoms was allowed if target lesions outside the radiotherapy field existed. Patients eligible for enrolment had to provide archival tumour biopsy tissue or underwent a fresh (pretreatment) tumour biopsy that was used to assess the level of HER3 protein expression by immunohistochemistry (IHC) and central pathology review.

Study drug administration

All patients were administered 800 mg of lumretuzumab intravenously in combination with 6 mg/mL \times min AUC of carboplatin and 200 mg/m² of paclitaxel every 3 weeks for 4–6 cycles. Thereafter, patients could receive lumretuzumab as a monotherapy (carboplatin and paclitaxel could be continued at the investigator's discretion) until disease progression, death, unacceptable toxicity, withdrawal of consent or at the investigator's decision, whichever occurred first. For carboplatin and paclitaxel, premedication was administered according to the manufacturer's instructions. For lumretuzumab, no premedication was foreseen prior to the first administration but could be introduced for subsequent cycles based on the patient's tolerability.

Tumour response and safety

Tumour response assessment using Response Evaluation Criteria in Solid Tumours V.1.1²³ was conducted at

screening and every 6 weeks thereafter by the investigators. CRs and PRs had to be confirmed with a second assessment.

Safety assessments included physical (ECOG performance status, vital signs) and laboratory examinations and ECG. AEs were defined according to the Common Terminology Criteria for Adverse Events, V.4.0 (CTCAE V.4.0).

Biomarker assessments

Squamous cell carcinoma antigen (SCC) and cytokeratin fragment (CYFRA) 21-1 from peripheral blood were locally assessed by immunoassay every 6 weeks.

Fresh or archival tumour biopsies were collected during screening. HER3 protein expression was assessed using an IHC assay as described previously¹⁴. Heregulin mRNA expression was measured by quantitative real-time PCR assay, as a potential predictive biomarker for lumretuzumab activity, in formalin-fixed paraffin-embedded (FFPE) sections obtained from fresh tumour biopsies collected from all patients at screening prior to initiation of treatment.²⁴ A prototype diagnostic assay was used for which reagents were prepared in a good manufacturing practice facility, the assay run using a z480 PCR system and calculation of Ct values was performed using validated diagnostic software (Q2 Solutions (Livingston, UK)). Patients were assigned as having high heregulin, if mRNA concentrations were greater than median heregulin expression previously determined using 150 primary FFPE tumour biopsy samples obtained from patients diagnosed with sqNSCLC.

Statistical considerations

All patients who received at least one dose of study medication were included in the statistical analyses. Descriptive statistics were used for demographics and safety as well as efficacy. In addition, in order to explore the relation between heregulin levels and response as well as whether responders and non-responders have different tumour marker dynamics, additional plots are shown.

RESULTS

Patients

Patient demographics and baseline characteristics are presented in [table 1](#). Altogether, 12 patients were enrolled. None of them had prior surgery for their disease and only two patients (16.7%) had prior radiotherapy. All 12 patients (100%) received at least one dose of the study treatment. The most common reason for discontinuation from the study was disease progression (9/12 patients (75%)). Other reasons for discontinuation were AE (general physical health deterioration; 1/12 patients (8.3%)), physician decision (1/12 patients (8.3%)) and other reason (1/12 patients (8.3%)). The median number of treatment cycles administered per patient was 5.5 cycles (range 1–16) for lumretuzumab and four cycles (range 1–6) for both carboplatin and paclitaxel. HER3 was present on tumour cells in 9/12 patients (75%),

Table 1 Baseline patient demographics and characteristics

Characteristic	Patients (N=12)
Sex, n (%)	
Male	10 (83.3)
Female	2 (16.7)
Age (years), median (range)	66.5 (52–74)
ECOG score, n (%)	
0	5 (41.7)
1	7 (58.3)
Prior radiotherapy, n (%)	2 (16.7)
Prior surgery, n (%)	0

ECOG, Eastern Cooperative Oncology Group.

although median expression was low (mean immunoreactive score (IRS): 0.25, range 0–1.47). HER3 expression was not detectable by IHC in 2/3 (66%) patients with a PR.

Safety

All 12 patients (100%) experienced at least one AE in the study ([table 2](#)). There were no deaths due to AEs. The most common AEs (>40% of patients) were diarrhoea (9/12 patients (75%)), asthenia (8/12 patients (66.7%)) and neurotoxicity (5/12 patients (41.7%)). Five of 12 patients (41.7%) had nine AEs of CTCAE grade 3 (anaemia (two events), neutropenia (two events), thrombocytopenia; respiratory tract infection, loss of consciousness, dyspnoea and general physical health deterioration (one event each)). Two patients also experienced two AEs of grade 4 (neutrophil count decreased and platelet count decreased). One of 12 patients (8.3%) had an AE (deterioration of general physical health, considered unrelated to lumretuzumab) leading to withdrawal from the study treatment. A total of 3/12 patients (25%) experienced four serious adverse events (SAEs). The four SAEs were respiratory tract infection and loss of consciousness experienced by one patient and infected neoplasm and dyspnoea experienced by one patient each all considered unrelated to study treatment.

Antitumour activity

The ORR and disease control rate (DCR) were 25% (90% CI 4.44 to 45.56) and 91.7% (90% CI 78.54 to 100), respectively ([table 3](#)). The best response was a PR seen in 3/12 patients (25%), and 8/12 patients (75%) had stable disease as a best response ([figure 1](#)). The median duration of PFS was 122 days (95% CI 81 to 217) with 10/12 patients (83.3%) showing disease progression during the study. There were 2/12 patients (16.7%) without any progression events, who were censored from the analysis of progression-free survival (PFS). The duration of the PR in patients was 81, 177 and 207 days, respectively. Tumour shrinkage in patients was accompanied by decreasing levels of CYFRA 21-1 but less so for SCC ([figure 2](#)).

Table 2 Summary of adverse events of any grade and of grade ≥ 3 adverse events

Adverse event	Patients (n) having an adverse event (%) (N=12)	
	All grades	Grade ≥ 3
Diarrhoea	9 (75.0)	0
Asthenia	8 (66.7)	0
Platelet count decreased	5 (41.7)	2 (16.7)
Neurotoxicity	5 (41.7)	0
Infusion-related reaction*	4 (33.3)	0
Nausea	4 (33.3)	0
Neutropenia	3 (25.0)	2 (16.7)
Anaemia	3 (25.0)	2 (16.7)
Dyspnoea	3 (25.0)	1 (8.3)
Respiratory tract infection	3 (25.0)	1 (8.3)
Constipation	3 (25.0)	0
Weight decreased	3 (25.0)	0
Decreased appetite	3 (25.0)	0
Alopecia	3 (25.0)	0
Insomnia	3 (25.0)	0
Rash	3 (25.0)	0
Abdominal pain	2 (16.7)	0
Abdominal pain upper	2 (16.7)	0
Stomatitis	2 (16.7)	0
Vomiting	2 (16.7)	0
Fatigue	2 (16.7)	0
Musculoskeletal pain	2 (16.7)	0
Pain in the extremity	2 (16.7)	0
Hypomagnesemia	2 (16.7)	0

Only adverse events reported by $>10\%$ of the patients are shown.

*Four patients had infusion-related reactions; three of which the investigator considered as related to lumretuzumab and one patient had an infusion-related reaction related to paclitaxel.

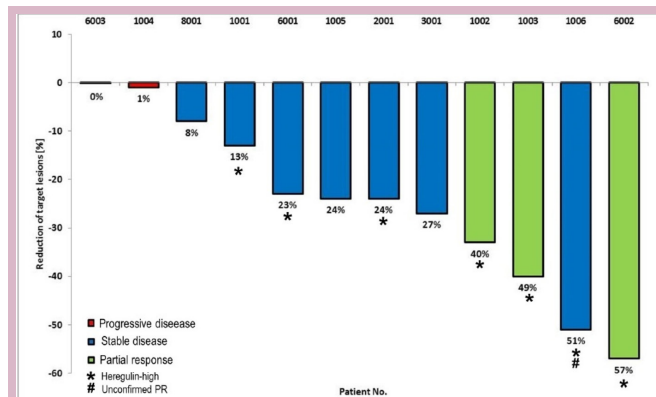
Heregulin mRNA–response relationships

Heregulin mRNA expression and response evaluation criteria in solid tumours response data was available for all patients (figure 3). Seven patients were considered heregulin high using the median ΔCt as a cut-off, determined from the analysis of a cohort of 150 FFPE tumour samples from patients with sqNSCLC as reported previously.²⁴

Table 3 Tumour response to treatment (RECIST)

	HRG low (N=5)	HRG high (N=7)	All patients (N=12)
Objective response rate, N (%)	0	3 (42.9)	3 (25.0)
Disease control rate, N (%)	4 (80.0)	7 (100)	11 (91.7)
PFS, median (95% CI), days	100 (38, 196)	122 (65, 217)	122 (81, 217)

HRG, heregulin; PFS, progression-free survival; RECIST, response evaluation criteria in solid tumours.

**Figure 1** Best percentage change from baseline in sum of target lesions.

All three patients with a PR were in the heregulin-high group. Hence, the ORR in the heregulin-high population was 42.9%, the DCR was 100% (7/7 patients) and the median PFS (95% CI) was 122 (65 to 217) days compared with an ORR of 0% (0/5 patients), a DCR of 80.0% (4/5 patients) and a median PFS (95% CI) of 100 (38 to 196) days for the remaining heregulin-low patients.

DISCUSSION

This is the first study to describe the combination of an anti-HER3 monoclonal antibody, lumretuzumab, with standard-of-care chemotherapy, that is, paclitaxel and carboplatin, as a first-line treatment for patients with sqNSCLC. In addition, the study aimed to generate signals in patients with elevated heregulin expression levels.

Overall, the safety profile of lumretuzumab in combination with carboplatin and paclitaxel in patients with advanced sqNSCLC is acceptable and consistent with carboplatin/paclitaxel chemotherapy toxicities. The most common AEs in this study were gastrointestinal, haematological and nervous system toxicities similar to the well-known side effects of carboplatin/paclitaxel chemotherapy alone.^{25–28} The addition of lumretuzumab to carboplatin and paclitaxel may have caused an increase in the incidence of diarrhoea compared with chemotherapy alone. Overall, this combination appeared to be tolerable as the median number of cycles given for chemotherapy was similar to the one seen by others.^{25 26 28} An increased incidence of diarrhoea has been previously described for lumretuzumab

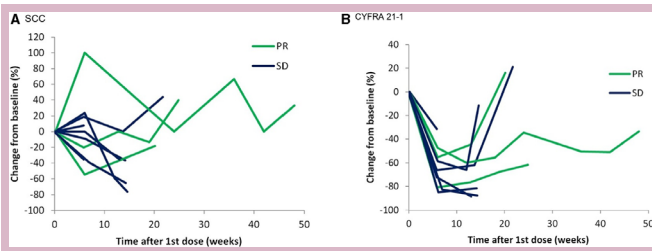


Figure 2 Tumour marker dynamics: percentage change from baseline, measured in plasma.

monotherapy and combinations of lumretuzumab with cetuximab, erlotinib and pertuzumab.^{14 24 29} An increased incidence of diarrhoea was also observed with other HER3-targeting agents, seribantumab and patritumab, when combined with erlotinib, for the treatment of NSCLC in phase II studies.^{30 31} Nevertheless, no diarrhoea grade ≥ 3 event has been reported for the combination of lumretuzumab with chemotherapy in the present study.

The efficacy seen with the combination of lumretuzumab in combination with carboplatin and paclitaxel, ORR=25% and a median PFS=122 days, is similar to

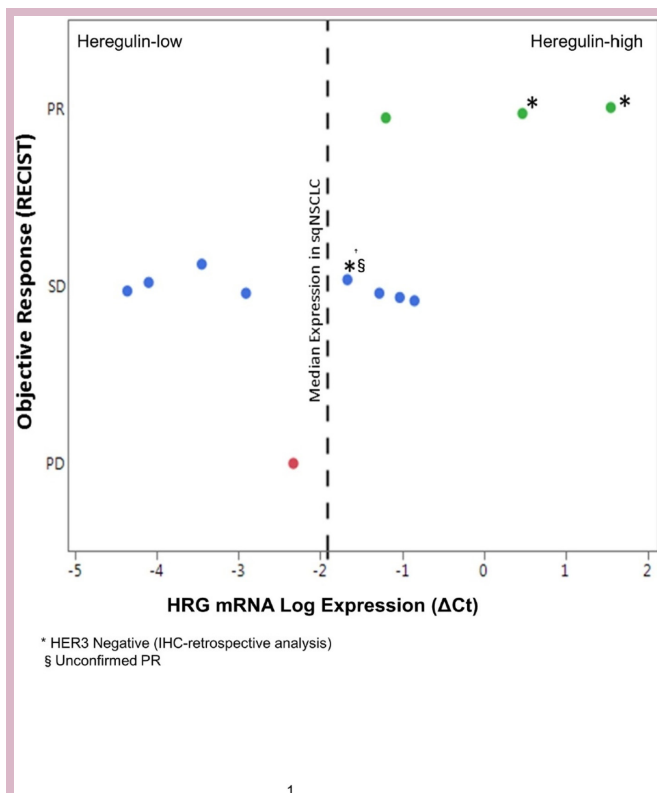


Figure 3 Objective response and HRG mRNA log expression in patients with first-line sqNSCLC (n=12). Green indicates partial response; blue indicates stable disease and red indicates progressive disease. HRG mRNA log expression determined using the prototype diagnostic assay. HER3, human epidermal growth factor receptor 3; HRG, heregulin; PR, partial response; mRNA, messenger RNA; sqNSCLC, squamous non-small cell lung cancer.

what has been published for chemotherapy alone in recent phase III studies.^{25–28} Certainly, due to the low number of patients treated in this study, the efficacy data should be interpreted cautiously.

Clinical phase II studies using HER3-targeting therapies^{32–37} have suggested heregulin mRNA expression levels as a response-predictive biomarker for HER3-targeting therapy. In particular, patients with sqNSCLC have been shown to express higher levels of heregulin per se.²⁰ Indeed, all three partial responders described in this study were considered to have higher heregulin expression levels; hence, the level of heregulin expression may enrich for patients with objective responses and a higher DCR. However, the number of patients responding to treatment were too small to draw firm conclusions in this regard and duration of response in patients with high tumour heregulin levels was in the range of what can be expected for chemotherapy alone.³⁸ This is in line with phase II studies in NSCLC, colorectal cancer and head and neck cancer that could not show any treatment benefit of HER3-targeting therapies in heregulin-high subgroups.^{31 39 40} An ongoing phase II study of HER3-targeting seribantumab in combination with docetaxel or pemetrexed in second to third-line treatment, prospectively heregulin-positive tested and selected patients with NSCLC might shed more light on this issue.⁴¹ The clinical activity in this small phase I patient set is overall inferior to the recent phase III trials including checkpoint inhibition in advanced/metastatic NSCLC. Pembrolizumab monotherapy in patients with PD-L1 expression ($\geq 50\%$) with sqNSCLC or non-squamous NSCLC achieved an ORR of 44.8%,⁹ pembrolizumab in combination with chemotherapy in patients with sqNSCLC had an ORR of 57.9% with a median duration of response of 7.7 months¹¹ and atezolizumab in combination with chemotherapy in patients with sqNSCLC showed an ORR of 49% and a median duration of response of 7.2 months.³⁸ Eventually, the present data and the outcome of a sister study testing the combination of lumretuzumab plus erlotinib in patients with metastatic/advanced NSCLC showing similar limited efficacy²⁴ led to the decision not to execute the phase II portion of this study.

In conclusion, combination treatment of lumretuzumab with carboplatin and paclitaxel was well tolerated, but clinically meaningful contribution to efficacy by lumretuzumab could not be demonstrated. High heregulin expression levels may be used to enrich for patients more likely to benefit, although the number of patients responding to treatment were too small to verify this hypothesis. Overall, the results of the present study indicate that HER3 is not a strong enough driver for sqNSCLC to warrant further clinical development of lumretuzumab in this indication.

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