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Circulating heregulin level is associated with the efficacy of patritumab combined with erlotinib in patients with non-small cell lung cancer

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ABSTRACT

Objectives: Patritumab is a fully human anti-human epidermal growth factor receptor 3 (HER3) antibody that blocks activation by its ligand, heregulin (HRG). Preclinical studies have demonstrated the efficacy of patritumab in aberrantly high HRG-expressing non-small cell lung cancer (NSCLC). In the phase II randomized, placebo-controlled double-blind study HERALD ($n = 212$ patients with NSCLC), patritumab plus erlotinib did not improve progression-free survival (PFS) compared with placebo plus erlotinib. The current study examined whether soluble HRG (sHRG) level in serum correlated with the efficacy of patritumab plus erlotinib.
Materials and methods: Serum was obtained from participants prior to treatment ($n = 202$). sHRG level was measured using a validated quantitative immune assay, and correlations with survival were blindly assessed.
Results: sHRG level was various (−1346–11,772 pg/mL). Participants were divided into the sHRG-high or -low subgroups at the concentration defining near the third quartile, 980 pg/mL. Patritumab plus erlotinib significantly improved PFS relative to placebo in the sHRG-high subgroup ($n = 46$, hazard ratio 0.42 [0.19–0.96], $p = 0.0327$). In contrast, the HRG-low subgroup ($n = 148$) had no improvement in PFS with patritumab.
Conclusion: sHRG seems to be a predictive biomarker for the efficacy of patritumab plus erlotinib in NSCLC patients.

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1. Introduction

Human epidermal growth factor receptor (HER) 3 is overexpressed in and associated with poor prognosis in cancer such as non-small cell lung cancer (NSCLC) [1,2]. HER3 is activated by heregulin (HRG), aberrantly produced by cancer cells or cancer-associated fibroblast cells in an autocrine or paracrine fashion [3,4]. HER3 preferentially couples with other members of the HER family, especially HER2, and transduces the intracellular signal for anti-apoptosis or cell proliferation [5]. Furthermore, HER3-mediated intracellular signaling causes resistance to epidermal growth factor receptor (EGFR) inhibitors in cancer cells [6–8]. HER3 targeting agents are currently being intensively developed for oncotherapy [3,9–11].

Patritumab is a fully human anti-HER3 monoclonal antibody [9]. Patritumab binds to the HER3 extracellular domain and prevents ligand-dependent HER3 activation in cancer cells. Pre-clinical examination of 48 NSCLC cell lines observed that some were sensitive to patritumab both in vitro as well as in a xenograft model [9]. The patritumab-sensitive NSCLC cell lines expressed a significantly higher *HRG* mRNA level compared to non-sensitive cell lines.

Abbreviations: HER3, human epidermal growth factor receptor 3; NSCLC, non-small cell lung cancer; HRG, heregulin; EGFR, epidermal growth factor receptor; ITT, intent-to-treat; qRT-PCR, quantitative reverse transcription polymerase chain reaction.

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NSCLC cell lines with aberrant also produced a high amount of HRG as measured in the culture medium; this subsequently activated HER3 and the downstream effector Akt in an autocrine fashion [9]. Patritumab prevents HER3 and Akt phosphorylation in NSCLC cells with aberrantly high *HRG* expression but not in other NSCLC cell lines [9].

Erlotinib is an EGFR tyrosine kinase inhibitor that significantly improved survival in patients with NSCLC, especially those with an EGFR-activating mutation in the tyrosine kinase domain [12,13]. In contrast to its effect in cells with the *EGFR* mutation, erlotinib has significant but limited efficacy in NSCLC with the wild-type *EGFR* gene [14–16]. There is currently a need to evaluate erlotinib in combination with other drugs for improving treatment efficacy for NSCLC with wild-type *EGFR*.

In a phase I clinical study, patritumab alone or with combination therapy was well tolerated in patients with NSCLC [17,18]. A subsequent phase II randomized, placebo-controlled double-blind study (HERALD, NCT02134015) was conducted to assess the efficacy of low- or high-dose patritumab combined with erlotinib (patritumab plus erlotinib) in NSCLC [19]. Patritumab plus erlotinib did not prolong PFS compared with placebo plus erlotinib in an intent-to-treat (ITT) population. However, patritumab plus erlotinib significantly improved PFS in participants with high *HRG* mRNA expression in tumor tissue [19,20]. In contrast to participants with high *HRG* mRNA expression, participants with low *HRG* mRNA expression had no significant improvement in PFS with patritumab plus erlotinib as compared to placebo plus erlotinib. It was concluded that HRG was a predictive biomarker for the efficacy of patritumab. Based upon these results, a 2-part phase III randomized, placebo-controlled double-blind study, HER3-LUNG, was initiated to test the efficacy of patritumab plus erlotinib in patients with high tumor *HRG* mRNA NSCLC [21].

The HERALD study previously evaluated tumor HRG mRNA expression and its correlation with the efficacy of patritumab combination therapy. The current study aimed to examine whether the soluble HRG (sHRG) protein level in serum would also correlate with the efficacy of patritumab plus erlotinib.

2. Material and methods

2.1. Study design

Patients were eligible for enrollment in the HERALD study if they had histologically confirmed NSCLC with stage IIIB/IV, measurable disease (per Response Evaluation Criteria in Solid Tumors guidelines, version 1.1) and documented disease progression or recurrence on at least one prior chemotherapy treatment [22]. Other eligibility criteria included an Eastern Cooperative Oncology Group performance status of 0 or 1 and adequate hematologic, hepatic, and renal function. Approximately 215 patients were randomized to one of three pre-planned arms: high-dose patritumab (18 mg/kg intravenously [IV] every 3 weeks [q3w]) with erlotinib (150 mg/day orally), low-dose patritumab (18 mg/kg IV loading dose, followed by 9 mg/kg q3w) with erlotinib (150 mg/day per os), or placebo with erlotinib (150 mg/day per os). The primary objective was to assess PFS in the ITT population. The institutional review boards of the participating institutions approved the protocol. All patients provided written informed consent, including consent to provide serum and tissue samples to test for biomarkers predictive of the patritumab response.

2.2. Biomarker assay for sHRG

Serum samples were obtained from participants prior to treatment. sHRG was measured using a validated quantitative sandwich immune assay using a commercially available kit (Human HRG1-β1 Quantikine ELISA Kits, R&D Systems, Minneapolis, MN, USA) according to our modified method [3]. Specifically, a 96-well microplate was coated with anti-HRG1 β1 capture antibody, washed, and incubated with samples and standards. The plate was washed, probed with anti-HRG1 β1 detection antibody, and labeled with a chromogen. Finally, optical density of samples and standards was determined using a spectrophotometric microplate reader set to 450 nm. sHRG concentration of each sample was determined based on standard curves.

2.3. Biomarker assay for HRG mRNA

Patients were required to provide a fresh tumor sample prior to treatment or to make available archived tumor tissue. *HRG* mRNA expression was evaluated using a quantitative reverse transcription polymerase chain reaction (qRT-PCR) assay that was developed and validated by MolecularMD (Portland, OR) as described previously [20]. Briefly, total mRNA was extracted from formalin fixed embedded tissue, and cDNA was obtained from reverse transcription of the mRNA. Transcript levels of *HRG* and three reference genes were evaluated using qRT PCR.

2.4. Biomarker assay for EGFR sequencing

Mutations in the EGFR gene were analyzed in formalin-fixed paraffin-embedded tissue and plasma samples using the Qiagen EGFR RGQ PCR Kit (Germantown, MD) on the Qiagen Rotor-Gene Q 5plex HRM (Germantown, MD) instrument as described previously [20]. This kit will detect mutations on exon 18 (G719A, G719S, G719C), exon 20 (T790M, S768I), and exon 21 (L858R, L861Q), as well as exon 19 deletions and exon 20 insertions.

2.5. Statistical analyses

Kaplan-Meier curves were generated for PFS and OS and used to calculate medians and 95% CIs by treatment group. Two-sided p-values was based on stratified log-rank test and hazard ratios (and 95% CIs) were based on stratified Cox proportional hazard models, stratified by best response to prior therapy (CR/PR, SD, PD) and histology subtype (Adenocarcinoma vs. Non-Adenocarcinoma).

3. Results

3.1. Patient characteristics

Of the 215 patients, 212 received one of the three treatments: high-dose patritumab plus erlotinib ($n = 70$), low-dose patritumab plus erlotinib ($n = 71$), and placebo plus erlotinib ($n = 71$). These comprised the participants for the ITT analysis. The remaining three participants enrolled but did not receive a treatment and thus were excluded from the ITT analysis. Serum samples were collected in 202 patients who consented to a biomarker study for measuring sHRG. Among those patients, eight were not randomized and not treated with study drugs. Therefore, 194 patients were included in the assessment regarding the correlation between sHRG level and survival. sHRG distribution is demonstrated in Fig. 1. sHRG level was various ranged from −1346–11,772 pg/mL. The value defining the third quartile was 980 pg/mL, which was used as the cutoff value to determine the sHRG-high and sHRG-low populations. Baseline characteristics of the ITT population as well as the sHRG-high population are shown in Supplemental Table S1. Characteristics were similar between the two populations, although the sHRG-high population was more frequently diagnosed as adenocarcinoma than was the ITT population. sHRG-high participants in each treatment arm had similar baseline characteristics. Among the sHRG-high

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