1. ABSTRACT

Study Title

Tarlatamab vs. real-world physicians' choice of therapies in patients with relapsed or refractory small cell lung cancer (SCLC) after two or more prior lines of treatment: patient-level indirect treatment comparison (ITC) of DeLLphi-301 vs. Flatiron real-world data

Authors [redacted]

Affiliations: [1]Amgen Global HEOR, [2]Analysis Group

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Keywords

Patient-level ITC, tarlatamab, SCLC, third-line and beyond (3L+)

Rationale and Background

Evaluation of the comparative effectiveness of tarlatamab vs. comparator therapies is required for upcoming health technology assessment (HTA) and payer submissions seeking reimbursement of tarlatamab in 3L+ settings for SCLC. DeLLphi-301, a phase 2 open-label study is currently the only clinical trial of tarlatamab in the 3L+ setting. As the DeLLphi-301 trial does not have a concurrent comparator arm, an external control arm is required for assessment of comparative effectiveness.

External control arms can come from previous clinical trials or real-world data. In the absence of relevant clinical trials of comparator treatments in the 3L+ setting for SCLC, an external control arm from a suitable real-world data source is needed. The Flatiron Health Research Database (hereafter referred to as Flatiron data) was deemed a suitable data source for construction of an external control arm for tarlatamab because of its high-quality clinical data, sufficient sample size and reflection of a contemporaneous SCLC patient population.

In this study, we compared tarlatamab versus comparator therapies in 3L+ settings using patient-level data from DeLLphi-301 and Flatiron datasets. While rigorous methods based on aggregate data from Flatiron and other real-world sources of external controls have been used in previous ITC studies (study number: 20230204), analyses based entirely on patient-level data are recommended when feasible. Use of patient-level data offers several important advantages in this study, including: 1) applying key trial inclusion/exclusion criteria to select an external control arm that more closely matches the DeLLphi-301 trial population, 2) more comprehensively adjusting for differences in prognostic factors between tarlatamab and external control arms, and 3) conducting additional analyses to pressure test the conclusions of the previously conducted ITCs. Therefore, the patient-level comparative study proposed here is critical to comprehensively address evidence needs for HTA submissions in this 3L+ setting.

Research Question and Objectives

Objectives	Endpoints

Primary	
• To estimate the relative effect of tarlatamab vs. comparator therapies on overall survival (OS)	• OS
Secondary	
• To estimate the relative effect of tarlatamab vs. comparator therapies on time to treatment discontinuation (TTD)	• TTD
• To estimate the relative effect of tarlatamab vs. comparator therapies on time to next treatment or death (TTNTD)	• TTNTD
Exploratory	
• To estimate the relative effect of tarlatamab vs. comparator therapies on progression-free survival (PFS) • To estimate the relative treatment effect of tarlatamab vs. comparator therapies on objective response rate (ORR) • To estimate the relative treatment effect of tarlatamab vs. comparator therapies on OS and TTD, adjusted for post-progression use of tarlatamab	• PFS • ORR • OS, TTD (adjusted)

Study Design

A patient-level ITC was conducted to estimate the relative treatment effects of tarlatamab vs. comparator therapies among patients with relapsed or refractory SCLC who have progressed or recurred following one platinum-based regimen and at least one other LOT. Key patient eligibility criteria from the DeLLphi-301 trial were applied to Flatiron data to create an external control arm of patients receiving comparator therapies in the 3L+ setting for SCLC. Efficacy outcomes were compared between the tarlatamab and comparator therapies cohorts utilizing a propensity score (PS) weighting approach to adjust for differences in the distributions of key prognostic factors between these two cohorts.

Setting

3L+ setting for SCLC

Subjects and Study Size, Including Dropouts

A total of 97 patients from DeLLphi-301 who received 10 mg dose of tarlatamab as their 3L+ treatment and 184 patients from Flatiron who met key eligibility criteria from DeLLphi-301 and received comparator therapies for SCLC in 3L+ setting from Flatiron were included.

Data Source(s) and Methods

The study used patient-level data from patients who received tarlatamab at a target dose of 10 mg in Parts 1 and 2 of the DeLLphi-301 trial (data-cut: October 2, 2023) and data from patients (meeting key DeLLphi-301 eligibility criteria) in the Flatiron database

(January 1st, 2013 to October 31th, 2021) who received comparator therapies for SCLC in 3L+ settings.

For patients in the comparator therapies cohort who met eligibility criteria at more than one line of therapy (LOT), one eligible LOT (i.e., index line) was identified and included in the analysis using a PS based approach. After index line selection, efficacy outcomes were compared between the tarlatamab and comparator therapies cohorts. All outcomes were compared with and without applying PS weights to adjust for differences in the distribution of key prognostic factors between these two cohorts.

OS, PFS, TTD, and TTNTD were compared between tarlatamab and comparator therapy groups using unweighted and weighted Kaplan-Meier analyses and log rank tests. Hazard ratios were estimated using unweighted and weighted Cox proportional hazards models. ORR was compared between tarlatamab and comparator therapy groups using unweighted and weighted logistic regression models.

Patients in the DeLLphi-301 trial who had radiographic progression were allowed to continue tarlatamab treatment per investigators' judgement. As HTA evaluations will be based on expected efficacy when used until disease progression as per the intended label for tarlatamab, analyses to estimate OS and TTD mimicking a real-world treatment scenario of no post-progression tarlatamab use were conducted separately. OS and TTD data derived from these separate analyses was also used in this study to estimate the relative treatment effect of tarlatamab vs. comparator therapies adjusted for post-progression use of tarlatamab.

Three sensitivity analyses were conducted. First, PFS analyses were repeated considering only patients in the Flatiron datasets whose progression was determined based on radiographic evidence alone as PFS events. Second, analyses were repeated with adjustment for additional lower importance confounders to assess robustness of the observed relative treatment effects. Third, analyses were repeated comparing tarlatamab versus a Flatiron comparator cohort that excluded patients using lurbinectedin or PD-1/L1 containing regimens as their 3L+ therapies, in order to inform HTA submission in Canada, where these excluded therapies are not currently reimbursed for SCLC.

Results

Tarlatamab was associated with a statistically significantly lower hazard of death, progression or death, treatment discontinuation, and time to next treatment or death relative to comparator therapies. The hazard ratios (HR; 95% confidence interval [CI]) of tarlatamab versus comparator therapies after adjustment for differences in confounders were 0.45 (0.30, 0.68) for OS, 0.61 (0.43, 0.90) for PFS, 0.54 (0.40, 0.72) for TTD, and 0.45 (0.30, 0.66) for TTNTD. Tarlatamab was associated with a higher response rate compared to comparator therapies (adjusted odds ratio (95% CI) of ORR was 2.80 (1.44, 5.83)). In analyses adjusting for post-progression use of tarlatamab, the HR was 0.47 (0.31, 0.71) for OS and 0.72 (0.51, 1.05) for TTD. Sensitivity analyses showed similar results as the main analyses.

Discussion

The present study utilized patient-level data from DeLLPhi-301 and Flatiron to indirectly compare the treatment effect of tarlatamab vs. comparator therapies in 3L+ settings on OS, PFS, TTD, TTNTD, and ORR. In the main analysis, after adjustment for differences in confounders with high and medium importance, tarlatamab consistently demonstrated

more favorable outcomes across all endpoints, including OS, PFS, TTD, TTND, and ORR, as opposed to comparator therapies in Flatiron. Results for OS and TTD were very similar even after accounting for post-progression use of tarlatamab in DeLLphi-301. The robustness of the results in the main analysis were further confirmed across sensitivity analyses adjusting for additional confounders that were deemed lower priority (i.e., less likely to introduce confounding), using a stricter definition of PFS in the real-world cohort, and in analyses excluding certain comparator therapies.

Like all ITCs, results of this study should be interpreted in light of its limitations. First, data drawn from the Flatiron cohort reflected data abstracted from real-world EHRs, which may be more susceptible to measurement error. For instance, measurement error may exist in the real-world PFS and ORR measures in Flatiron due to variations in how progression and response were defined across community and academic centers and also between trial vs. real-world settings, though our sensitivity analyses of PFS suggest minimal impact of these differences. Second, while inclusion/exclusion criteria from DeLLphi-301 were applied to the Flatiron cohort to the extent possible, there is a possibility for selection bias, to the extent that any otherwise eligible Flatiron patients excluded because of missing data on certain criteria have different outcomes than patients who were included. Third, given the non-randomized nature of the study, bias due to unmeasured/unknown confounders cannot be definitively ruled out. However, given the size of the observed associations and rigorous adjustment for high and medium priority confounders, it is unlikely that these findings are entirely explained by residual or unmeasured confounding.

In conclusion, relative to comparator therapies, tarlatamab was consistently associated with significantly longer OS and PFS, higher ORR, and longer TTD and TTNTD across all analyses. Results from this study are indicative of a significant clinical benefit of tarlatamab for adult patients with ES-SCLC who experienced progression after platinum-based therapy and at least one other line of therapy, and suggest tarlatamab is a promising option to improve clinical outcomes in this patient population.

Marketing Authorization Holder(s)

Not applicable

Names and Affiliations of Principal Investigators

[redacted] (Amgen Global HEOR)

[redacted] (Analysis Group, Inc.)