Tarlatamab versus chemotherapy as second-line treatment for small cell lung cancer (SCLC): primary analysis of the phase 3 DeLLphi-304 study

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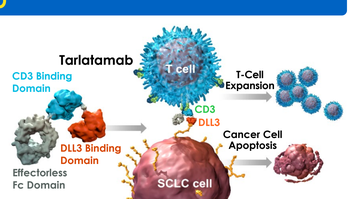
BACKGROUND

- Tarlatamab is a bispecific T-cell engager immunotherapy that directs cytotoxic T cells to DLL3-expressing SCLC cells resulting in tumor cell lysis[1]
- Tarlatamab demonstrated durable anticancer efficacy in patients with previously treated SCLC[2,3]
- Survival with current 2L chemotherapy options is modest and is also associated with substantial hematological toxicity[4–6]
- The DeLLphi-304 study was conducted to assess whether tarlatamab could improve survival for patients with SCLC whose disease had progressed or recurred following one line of platinum-based chemotherapy[7]
- We present results from the first planned interim analysis of the phase 3 DeLLphi-304 trial comparing tarlatamab to chemotherapy for 2L treatment of SCLC



KEY TAKEAWAYS

The DeLLphi-304 study affirms tarlatamab as the new standard of care in patients with previously treated SCLC

- In the phase 3 DeLLphi-304 study, tarlatamab significantly improved OS and PFS, reducing the risk of death by 40% compared with chemotherapy
- Tarlatamab, compared with chemotherapy, significantly improved patient-reported outcomes of dyspnea and cough
- Tarlatamab had a lower rate of high-grade AEs and lower rate of AEs that led to treatment discontinuations
- CRS and ICANS were mostly grade 1 or 2 in severity and generally manageable

CONCLUSIONS

The superior survival outcomes coupled with the favorable PROs and safety profile affirm tarlatamab as the standard of care for 2L treatment of SCLC

The DeLLphi-304 study establishes a new paradigm for bispecific T-cell engager immunotherapy in lung cancer

- Tarlatamab treatment achieved a 40% reduction in the risk of death compared to chemotherapy
- Benefit extended to those with poor prognostic factors such as platinum resistance and brain metastases
- Tarlatamab improved patient reported symptoms of dyspnea and cough compared with chemotherapy
- Tarlatamab was well tolerated with a lower incidence of high-grade AEs and a lower incidence of AEs that led to treatment discontinuations
- CRS and ICANS were mostly grade 1 or 2 in severity and generally manageable

DeLLphi-304 Phase 3 Study Design (NCT05740566)

Key inclusion criteria

- Histologically or cytologically confirmed SCLC
- Progression after 1L platinum-based chemotherapy +/- anti-PD-(L)1
- ECOG PS 0 or 1
- Asymptomatic, treated or untreated brain metastases

Randomization stratified by

- Prior anti-PD-(L)1 exposure (yes/no)
- CFI (< 90 days vs ≥ 90 to < 180 days vs ≥ 180 days)
- Presence of (previous/current) brain metastases (yes/no)
- Intended chemotherapy (topotecan/ amrubicin vs lurbinectedin)

Primary Endpoint: OS
Key Secondary Endpoints: PFS, PRO
Other Secondary Endpoints: OR, DC, DOR, safety

R 1:1 (N = 509)

- Tarlatamab (n = 254)
- Chemotherapy* (n = 255)

Topotecan (n = 185); Lurbinectedin (n = 47); Amrubicin (n = 23)

*Topotecan was used in all countries except Japan, lurbinectedin in Australia, Canada, Republic of Korea, Singapore and the United States, and amrubicin in Japan.

BASELINE PATIENT CHARACTERISTICS

	Tarlatamab (n = 254)	Chemotherapy (n = 255)
Median age, years (range)	64 (20 – 86)	66 (26 – 84)
Male / Female, %	72 / 28	66 / 34
Race Asian / Black / White, %	38 / 1 / 60	42 / 1 / 55
Smoking history Current or former smokers / Never smokers, %	91 / 9	88 / 12
ECOG performance status, 0 / 1, %	33 / 67	31 / 68
Prior anti-PD-(L)1 therapy, %	71	71
Prior radiotherapy for current malignancy*, %	63	63
Chemotherapy-free interval,% < 90 days ≥ 90 to < 180 days ≥ 180 days	43 33 24	45 31 25
Presence of brain / liver metastases, %	44 / 33	45 / 37
DLL3 expression, %, (n/N‡)	95 (207/217)	93 (198/214)

*Includes patients who received radiotherapy for brain metastases; ‡Number of patients with DLL3 expression (n) among patients with evaluable tumor tissue sample (N).

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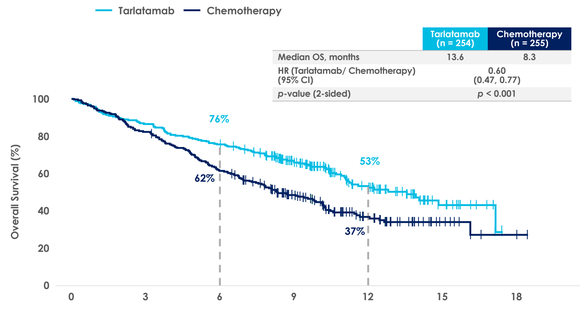
EFFICACY RESULTS

DeLLphi-304 met its primary endpoint with tarlatamab demonstrating superior overall survival over chemotherapy



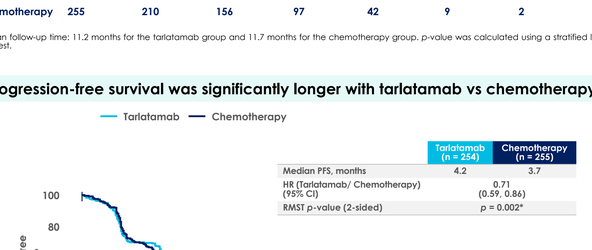
	Tarlatamab (n = 254)	Chemotherapy (n = 255)
Median OS, months	13.6	8.3
HR (Tarlatamab/ Chemotherapy) (95% CI)	0.60 (0.47, 0.77)	
p-value (2-sided)	*p* < 0.001	

Number of patients at risk:

Tarlatamab	254	220	192	131	60	17	0	
Chemotherapy	255	210	156	97	42	9	2	0

Median follow-up time: 11.2 months for the tarlatamab group and 11.7 months for the chemotherapy group. *p*-value was calculated using a stratified log-rank test.

Progression-free survival was significantly longer with tarlatamab vs chemotherapy



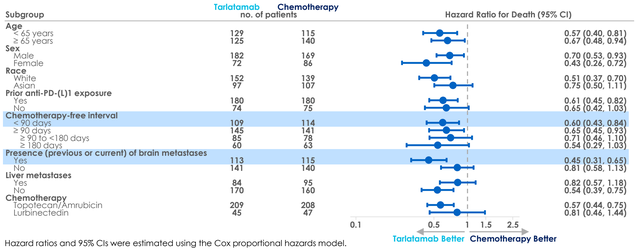
	Tarlatamab (n = 254)	Chemotherapy (n = 255)
Median PFS, months	4.2	3.7
HR (Tarlatamab/ Chemotherapy) (95% CI)	0.71 (0.59, 0.86)	
RMST *p*-value (2-sided)	*p* = 0.002*	

Number of patients at risk:

Tarlatamab	254	147	78	37	18	2	0	
Chemotherapy	255	137	56	15	3	0		

Median follow-up time: 11.0 months for the tarlatamab and the chemotherapy group. *The restricted mean PFS time in the tarlatamab and the chemotherapy group was 5.3 months and 4.3 months at 12 months respectively, resulting in statistically significant improvement of the tarlatamab group over the chemotherapy group.

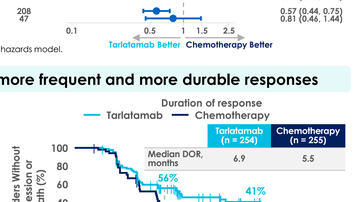
Survival benefit with tarlatamab was consistent across prespecified patient subgroups



Hazard ratios and 95% CIs were estimated using the Cox proportional hazards model.

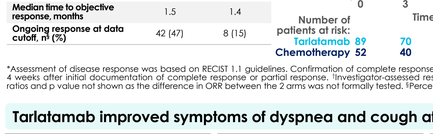
Tarlatamab was associated with more frequent and more durable responses

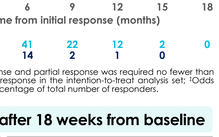
	Tarlatamab (n = 254)	Chemotherapy (n = 255)
Best overall response*†, n (%)		
Complete response	3 (1)	0 (0)
Partial response	86 (34)	52 (20)
Stable disease	84 (33)	112 (44)
Progressive disease	56 (22)	50 (20)
Not evaluable/no post-baseline scan	25 (10)	41 (16)
Objective response rate‡, % (95% CI)	35 (29, 41)	20 (16, 26)
Median duration of response, months	6.9	5.5
Median time to objective response, months	1.5	1.4
Ongoing response at data cutoff, n‖ (%)	42 (47)	8 (15)



*Assessment of disease response was based on RECIST 1.1 guidelines. Confirmation of complete response and partial response was required no fewer than 4 weeks after initial documentation of complete response or partial response. †Investigator-assessed response in the intention-to-treat analysis set; ‡Odds ratios and p value not shown as the difference in ORR between the 2 arms was not formally tested. ‖Percentage of total number of responders.

Tarlatamab improved symptoms of dyspnea and cough after 18 weeks from baseline



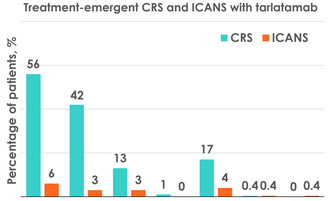


The mean difference in the change after 18 weeks in the physical functioning score (10.35 points [95% CI: 6.00, 14.69]) and the global health status score (6.93 points [95% CI: 5.04, 12.83]) trended in favor of tarlatamab. *Similar results were observed when the sensitivity analyses were carried out incorporating a more conservative estimand (ie., treatment policy strategy) for changes from baseline after 18 weeks in **dyspnea** (mean difference, −6.19; [95% CI, −8.88, −3.49]), **cough** (odds ratio, 1.48 [95% CI, 1.08, 2.02]), **chest pain** (odds ratio, 1.21 [95% CI, 0.80, 1.82]).

The change from baseline after 18 weeks in symptoms of chest pain, cough, and dyspnea were measured by European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ-C30) and the supplementary symptom scores for Lung Cancer (QLQ-LC13). Change from baseline after 18 weeks in chest pain and cough were analyzed using generalized linear mixed model (GLMM) with a cumulative logit link. Change from baseline after 18 weeks in dyspnea was analyzed using mixed effects model with repeated measures (MMRM) with a restricted maximum likelihood estimator method (REML). A hypothetical estimand strategy was pre-specified for these key secondary PRO endpoints. Clinically meaningful improvement in chest pain and cough was defined as improving at least 1 level in the response categories. Difference in dyspnea score between groups with more than 9 points is considered clinically meaningful.

SAFETY RESULTS

CRS and ICANS events were consistent with tarlatamab's established safety profile

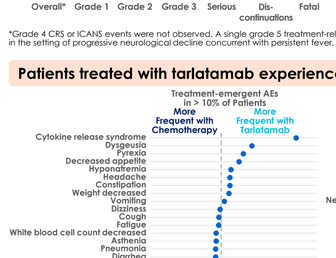


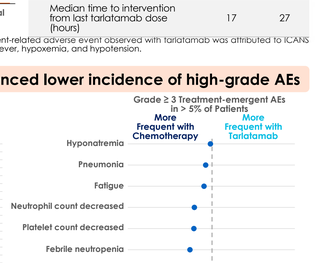
CRS with first two infusions

Tarlatamab (N = 252)	Minimum required monitoring duration: 6 - 8 Hours (n = 43)	48 Hours (n = 209)
Treatment emergent CRS, n (%)*	16 (37)	125 (60)
Grade 1	12 (28)	94 (45)
Grade 2	4 (9)	28 (13)
Grade 3	0 (0)	3 (1)
Serious adverse events	3 (7)	39 (19)
Leading to discontinuation of IP	0 (0)	1 (0.5)
Median time to intervention from last tarlatamab dose (hours)	17	27

*Grade 4 CRS or ICANS events were not observed. A single grade 5 treatment-related adverse event observed with tarlatamab was attributed to ICANS in the setting of progressive neurological decline concurrent with persistent fever, hypoxemia, and hypotension.

Patients treated with tarlatamab experienced lower incidence of high-grade AEs





AEs shown include AEs of interest for tarlatamab and selected known AEs for chemotherapy.

Tarlatamab had a more favorable safety profile

	Tarlatamab (n = 252)*	Chemotherapy (n = 244)*
Median duration of treatment, months, (range)	4.2 (< 1–17)	2.5 (< 1–15)
All grade, TEAEs, n (%)	249 (99)	243 (100)
All grade, TRAEs n (%)	235 (93)	223 (91)
Grade ≥ 3 TRAEs, n (%)	67 (27)	152 (62)
Serious TRAEs, n (%)	70 (28)	75 (31)
TRAEs leading to dose interruption and/or dose reduction, n (%)	48 (19)	134 (55)
TRAEs leading to discontinuation, n (%)	7 (3)	15 (6)
Treatment-related grade 5 events†, n (%)	1 (0.4)	4 (2)

*Safety analysis set (all patients who received at least one dose of study treatment). †The single grade 5 TRAE observed with tarlatamab was attributed to ICANS in the setting of progressive neurological decline concurrent with persistent fever, hypoxemia, and hypotension. Grade 5 TRAEs observed with chemotherapy were attributed to general physical health deterioration (n = 1), pneumonia (n = 1), respiratory tract infection (n = 1), and tumor lysis syndrome (n = 1).

References

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Abbreviations

1L, first-line; **2L**, second-line; **AE**, adverse event; **CD3**, cluster of differentiation 3; **CFI**, chemotherapy-free interval; **CI**, confidence interval; **CRS**, cytokine release syndrome; **DC**, disease control; **DLL3**, delta-like ligand 3; **DOR**, duration of response; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **Fc**, fragment crystallizable; **HR**, hazard ratio; **ICANS**, immune effector cell-associated neurotoxicity syndrome; **IP**, investigational product; **LS**, least squares; **OR**, objective response; **ORR**, OR rate; **OS**, overall survival; **PD-(L)1**, programmed death-(ligand) 1; **PFS**, progression-free survival; **PRO**, patient reported outcome; **R**, randomization; **RECIST**, Response Evaluation Criteria in Solid Tumors; **SCLC**, small cell lung cancer; **TEAE**, treatment-emergent adverse event; **TRAE**, treatment-related adverse event.

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