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

Charles M. Rudin, Giannis S. Mountzios, Longhua Sun, Byoung Chul Cho, Umut Demirci, Sofia Baka, Mahmut Gumus, Antonio Lugini, Tudor-Eliade Ciuleanu, Myung-Ju Ahn, Pedro Rocha, Bo Zhu, Fiona Blackhall, Tatsuya Yoshida, Taofeek K. Owonikoko, Luis Paz-Ares, Shuang Huang, Diana Gauto, Gonzalo Recondo, Martin Schuler

Speaker: **Charles M. Rudin, MD, PhD**, Fiona and Stanley Druckenmiller Center for Lung Cancer Research, Memorial Sloan Kettering Cancer Center, New York, USA.

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Key takeaways

In the phase 3 DeLLphi-304 study, tarlatamab significantly improved overall survival and progression-free survival, 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

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

CRS, cytokine release syndrome; **ICANS,** immune effector cell-associated neurotoxicity syndrome.

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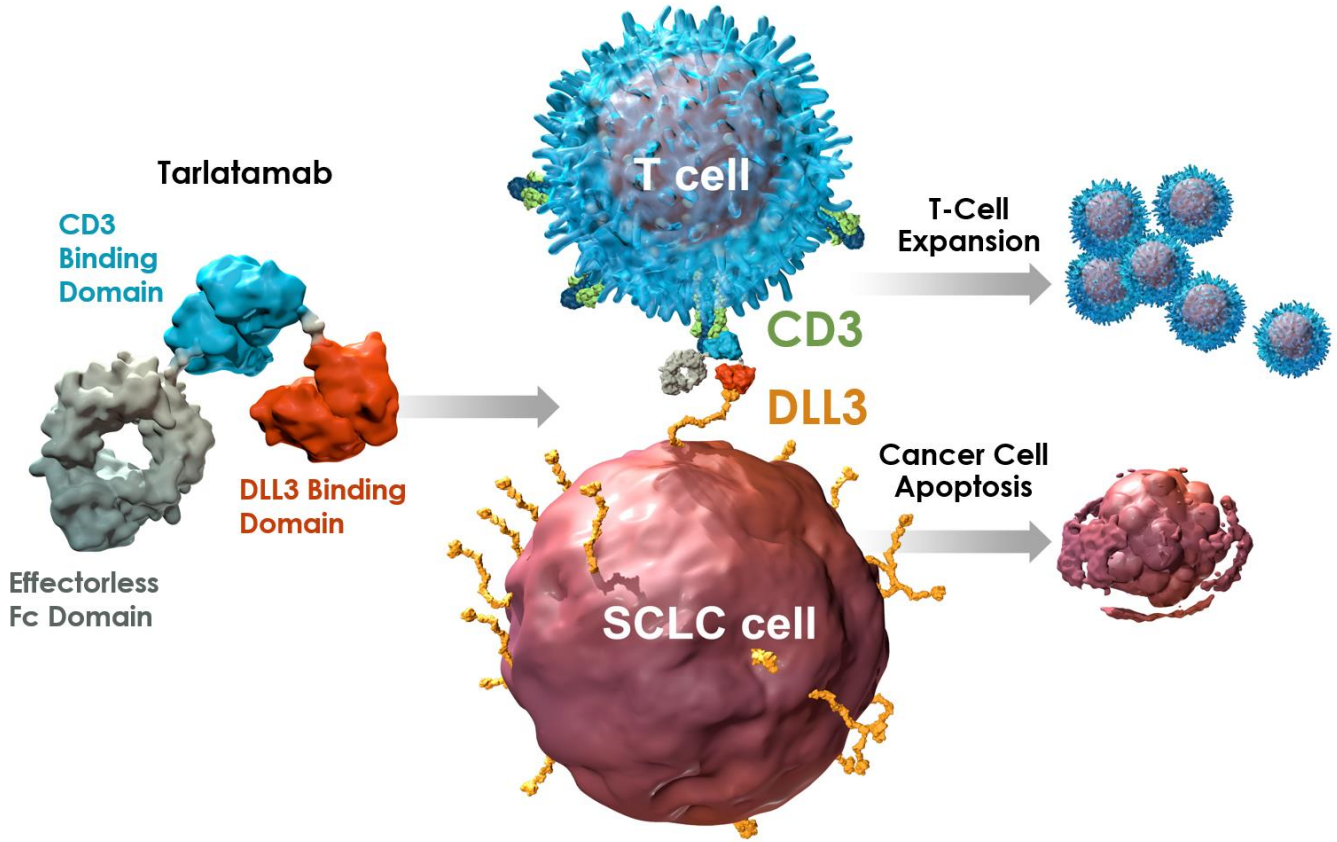
Background

- 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

2L, second-line; **CD3,** cluster of differentiation 3; **DLL3,** delta-like ligand 3; **Fc,** fragment crystallizable region; **SCLC,** small cell lung cancer.

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Randomized, controlled, phase 3 DeLLphi-304 study (NCT05740566)

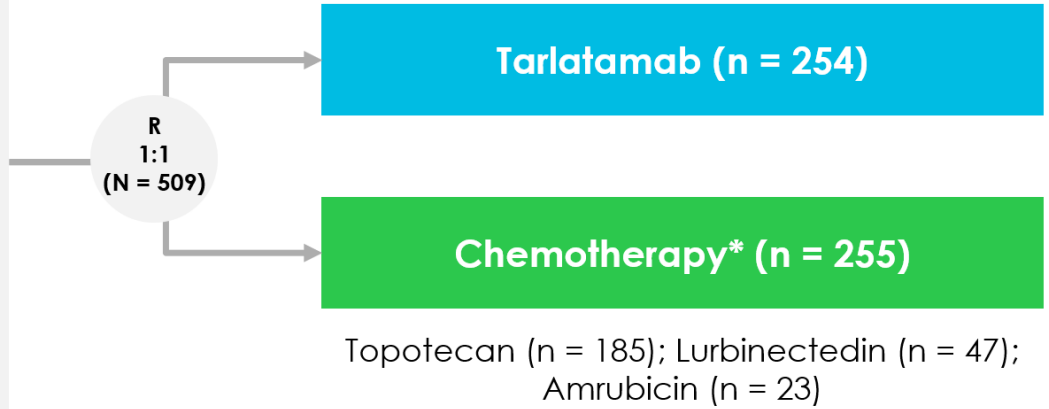
DeLLphi 304

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)
- Chemotherapy-free interval (< 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: Overall survival
Key Secondary Endpoints: Progression-free survival, patient-reported outcomes
Other Secondary Endpoints: Objective response, disease control, duration of response, safety

*Topotecan was used in all countries except Japan, lurbinectedin in Australia, Canada, Republic of Korea, Singapore and the United States, and amrubicin in Japan.
1L, first-line; **ECOG PS,** Eastern Cooperative Oncology Group performance status; **PD-(L)1,** programmed death (ligand)-1; **R,** randomization; **SCLC,** small cell lung cancer.

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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).
DLL3, delta-like ligand 3; **ECOG,** Eastern Cooperative Oncology Group; **PD-(L)1,** programmed death (ligand)-1.

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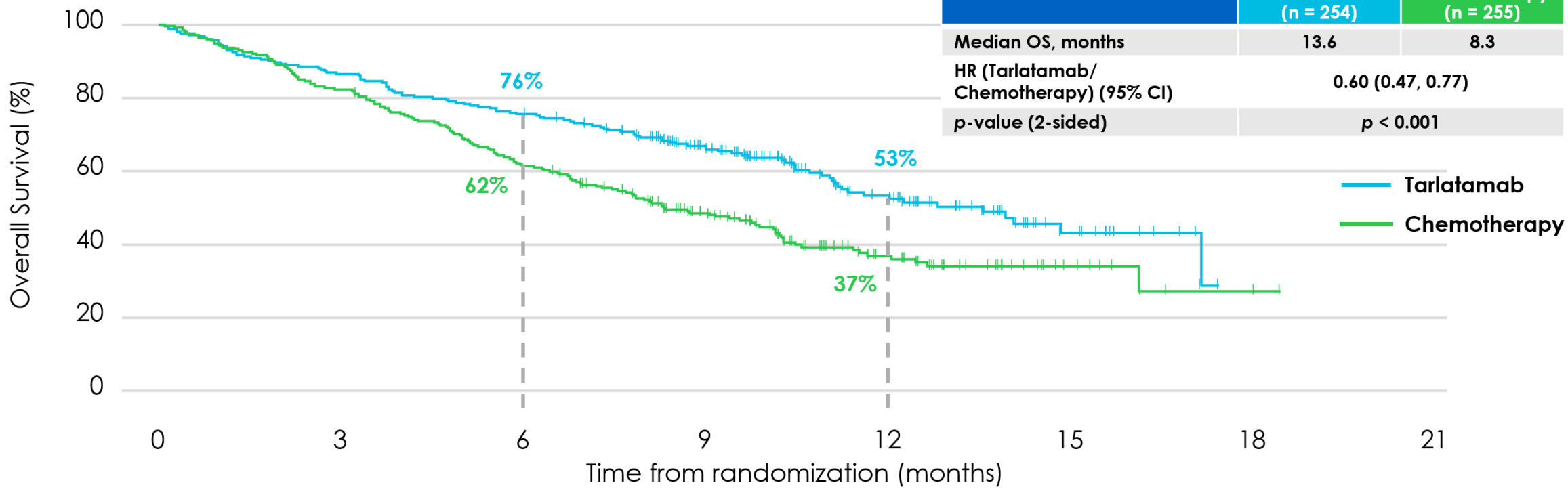
DeLLphi-304 met its primary endpoint with tarlatamab demonstrating superior overall survival over chemotherapy

	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.
HR, hazard ratio; **OS**, overall survival.

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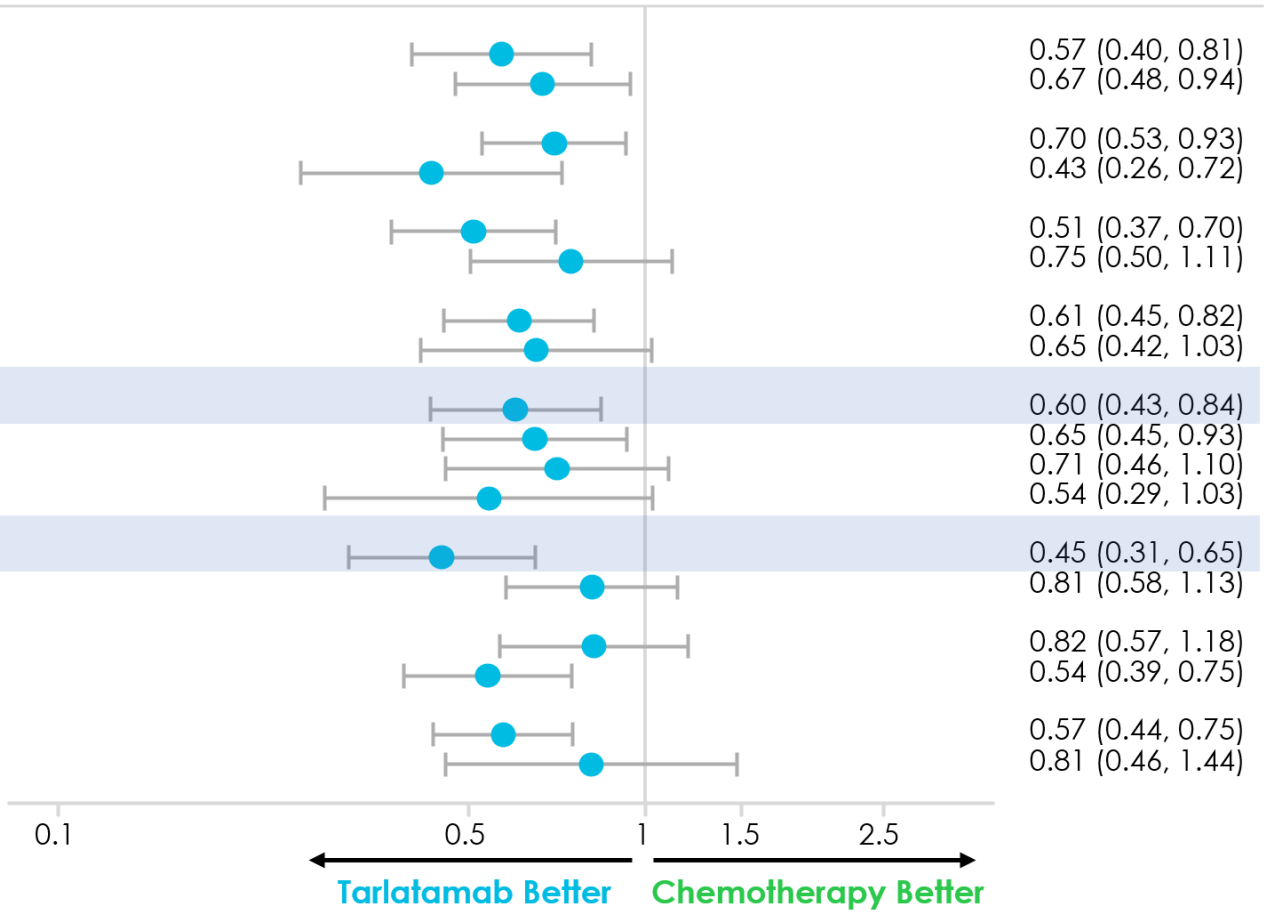
Survival benefit with tarlatamab was consistent across prespecified patient subgroups

Subgroup	Tarlatamab (no. of patients)	Chemotherapy (no. of patients)	Hazard Ratio for Death (95% CI)
Age			
< 65 years	129	115	0.57 (0.40, 0.81)
≥ 65 years	125	140	0.67 (0.48, 0.94)
Sex			
Male	182	169	0.70 (0.53, 0.93)
Female	72	86	0.43 (0.26, 0.72)
Race			
White	152	139	0.51 (0.37, 0.70)
Asian	97	107	0.75 (0.50, 1.11)
Prior anti-PD-(L)1 exposure			
Yes	180	180	0.61 (0.45, 0.82)
No	74	75	0.65 (0.42, 1.03)
Chemotherapy-free interval			
< 90 days	109	114	0.60 (0.43, 0.84)
≥ 90 days	145	141	0.65 (0.45, 0.93)
≥ 90 to <180 days	85	78	0.71 (0.46, 1.10)
≥ 180 days	60	63	0.54 (0.29, 1.03)
Presence (previous or current) of brain metastases			
Yes	113	115	0.45 (0.31, 0.65)
No	141	140	0.81 (0.58, 1.13)
Liver metastases			
Yes	84	95	0.82 (0.57, 1.18)
No	170	160	0.54 (0.39, 0.75)
Chemotherapy			
Topotecan/Amrubicin	209	208	0.57 (0.44, 0.75)
Lurbinectedin	45	47	0.81 (0.46, 1.44)



Hazard ratios and 95% CIs were estimated using the Cox proportional hazards model.
PD-(L)1, programmed cell death (ligand)-1.

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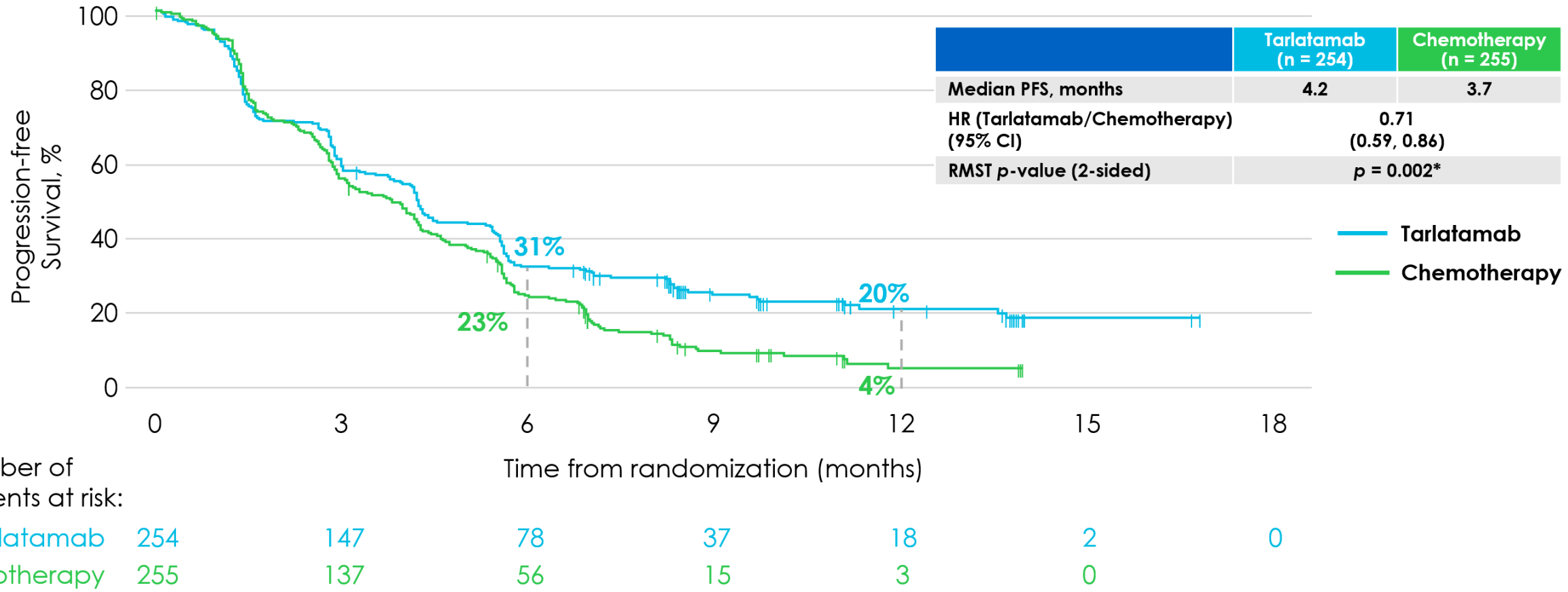
Progression-free survival was significantly longer with tarlatamab vs chemotherapy



	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.
HR: hazard ratio; **PFS,** progression-free survival.

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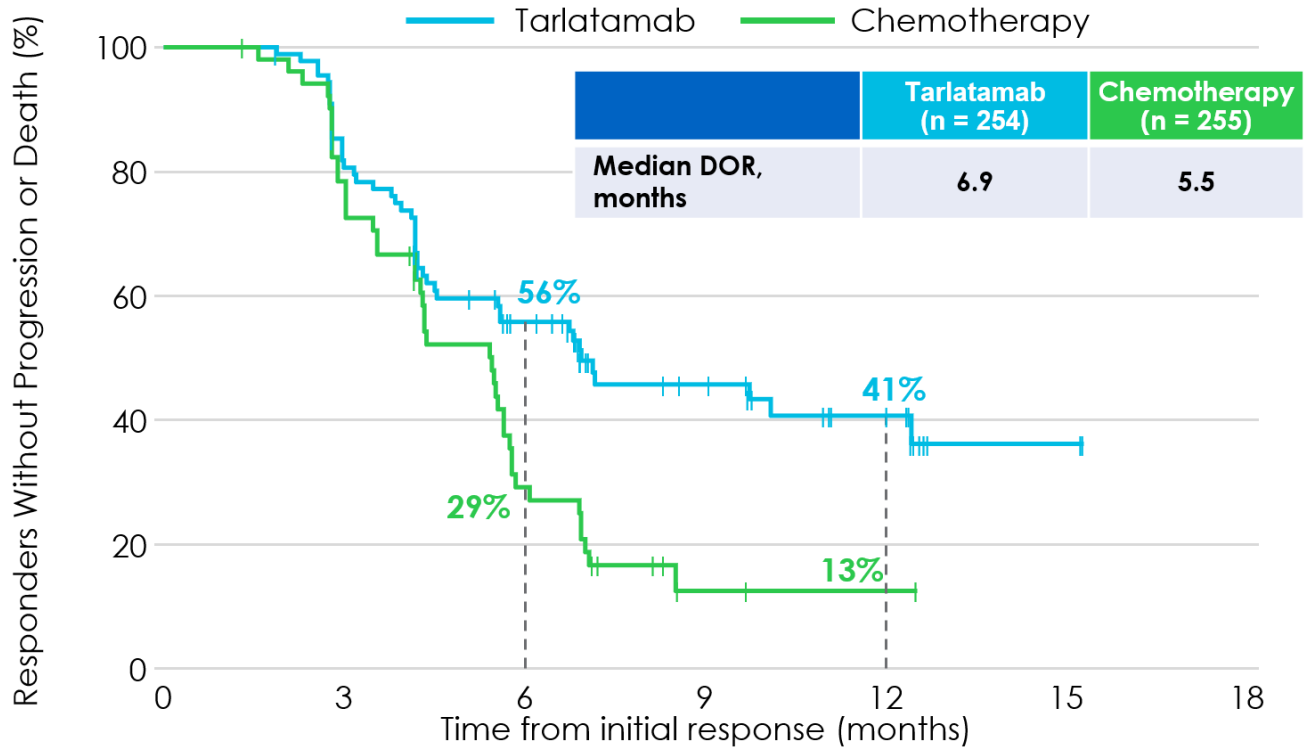
Tarlatamab was associated with more frequent and more durable responses

	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)

Duration of response



	Tarlatamab (n = 254)	Chemotherapy (n = 255)
Median DOR, months	**6.9**	**5.5**

Number of patients at risk:

Tarlatamab	89	70	41	22	12	2	0
Chemotherapy	52	40	14	2	1	0	

*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.
DOR, duration of response; **RECIST,** Response Evaluation Criteria in Solid Tumors.

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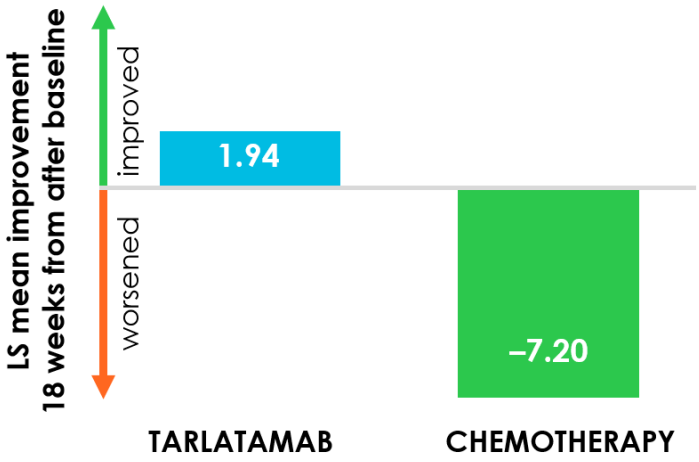
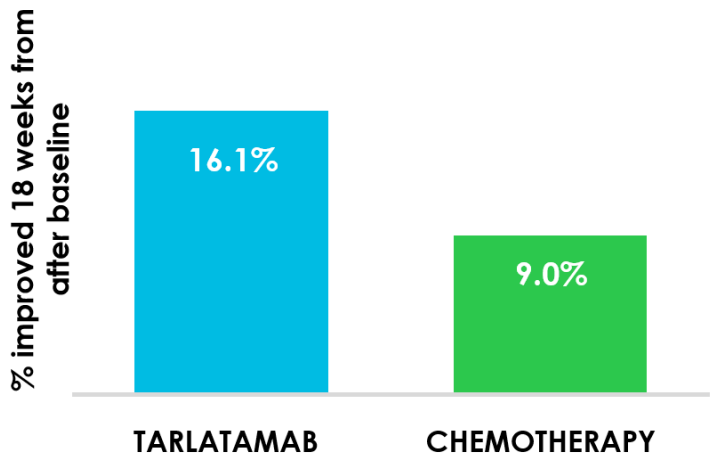
Tarlatamab improved symptoms of dyspnea and cough after 18 weeks from baseline

Dyspnea
mean improvement from baseline



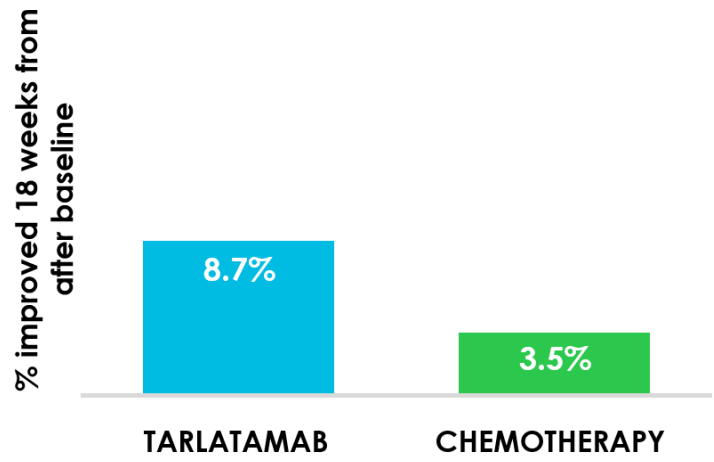
LS mean difference = -9.14*
95% CI (-12.64, -5.64)
***p* < 0.001**

Cough
% patients with symptom improvement



Odds ratio = 2.04*
95% CI (1.17, 3.55)
***p* = 0.012**

Chest Pain
% patients with symptom improvement



Odds ratio = 1.84*
95% CI (0.89, 3.81)
***p* = 0.1**
(Did not meet statistical significance)

The mean difference in the change after 18 weeks in the physical functioning score (10.35 points [95% CI: 6.00 to 14.69]) and the global health status score (8.93 points [95% CI: 5.04 to 12.83]) trended in favor of tarlatamab.
*Similar results were observed when the sensitivity analyses were carried out incorporating a more conservative estimand (i.e., treatment policy strategy) for change from baseline after 18 weeks in **dyspnea** (mean difference, -6.19; [95% CI, -8.88 to -3.49]), **cough** (odds ratio, 1.48 [95% CI, 1.08 to 2.02]),and **chest pain** (odds ratio, 1.21 [95% CI, 0.80 to 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.
LS, least squares.

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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).
ICANS, immune effector cell-associated neurotoxicity syndrome; **TEAE,** treatment-emergent adverse event; **TRAE,** treatment-related adverse event.

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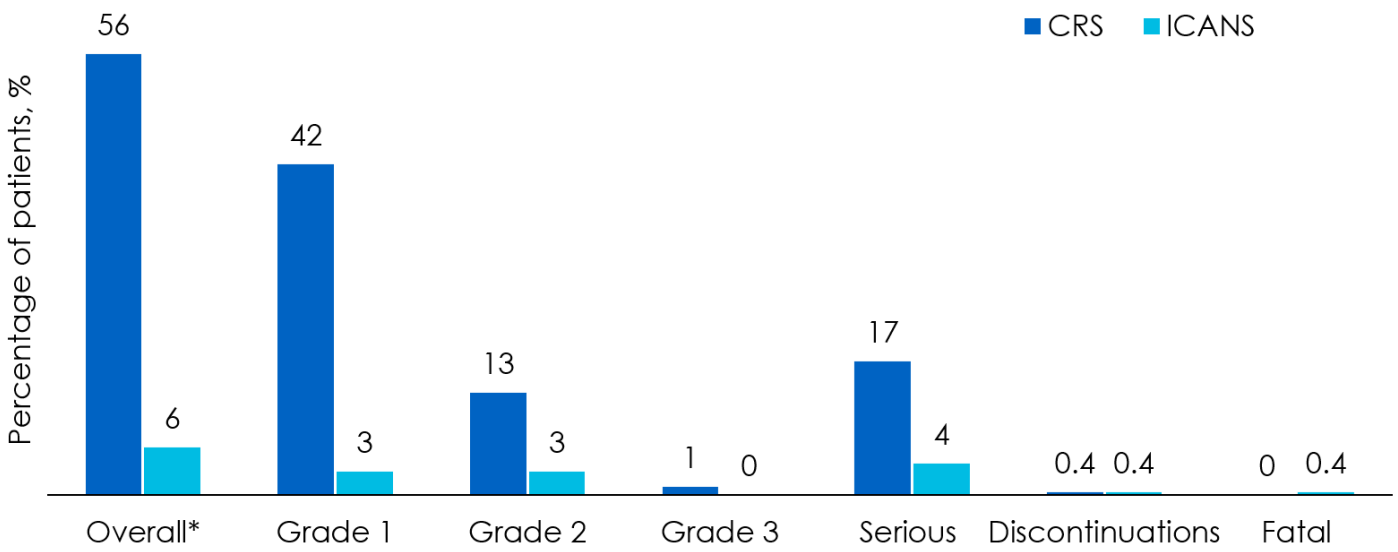
CRS and ICANS events were consistent with tarlatamab's established safety profile

Treatment-emergent CRS and ICANS with tarlatamab



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.

CRS, cytokine release syndrome; **ICANS,** immune effector cell-associated neurotoxicity syndrome; **IP**, investigational product.

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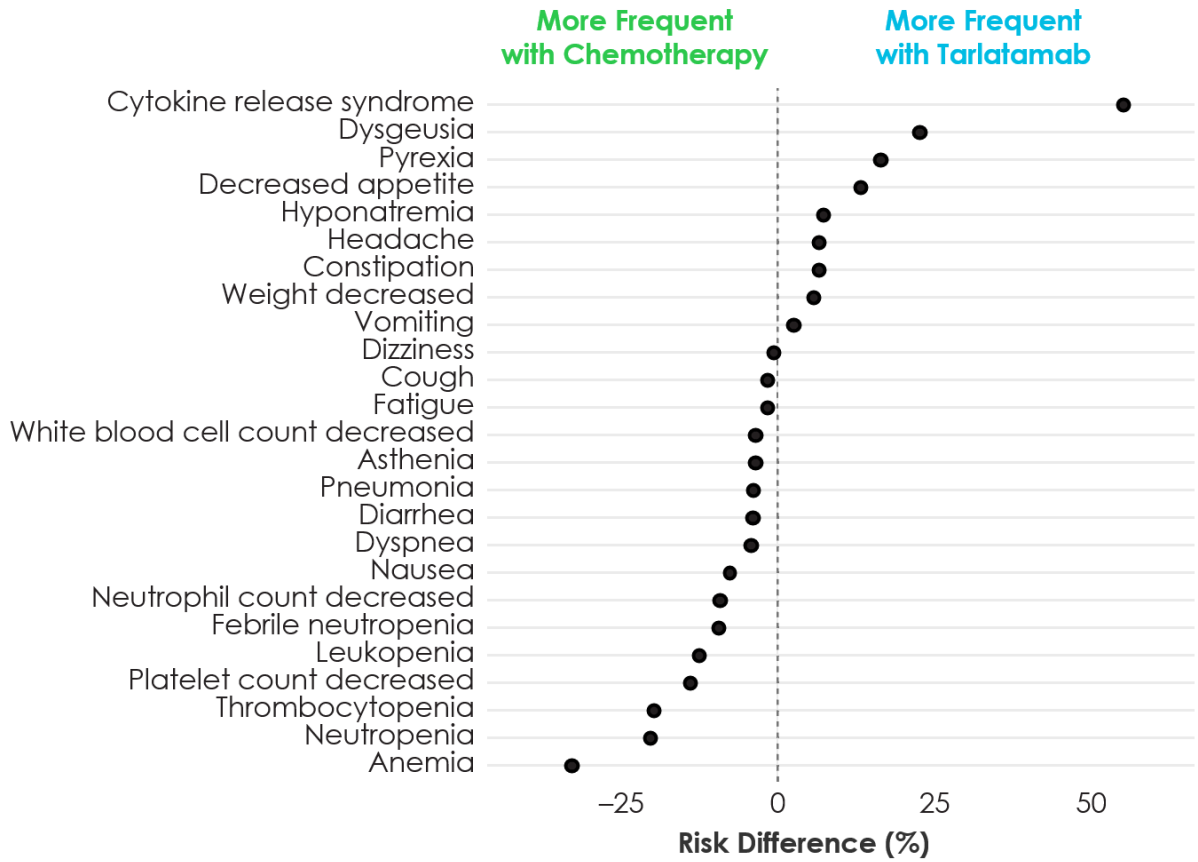
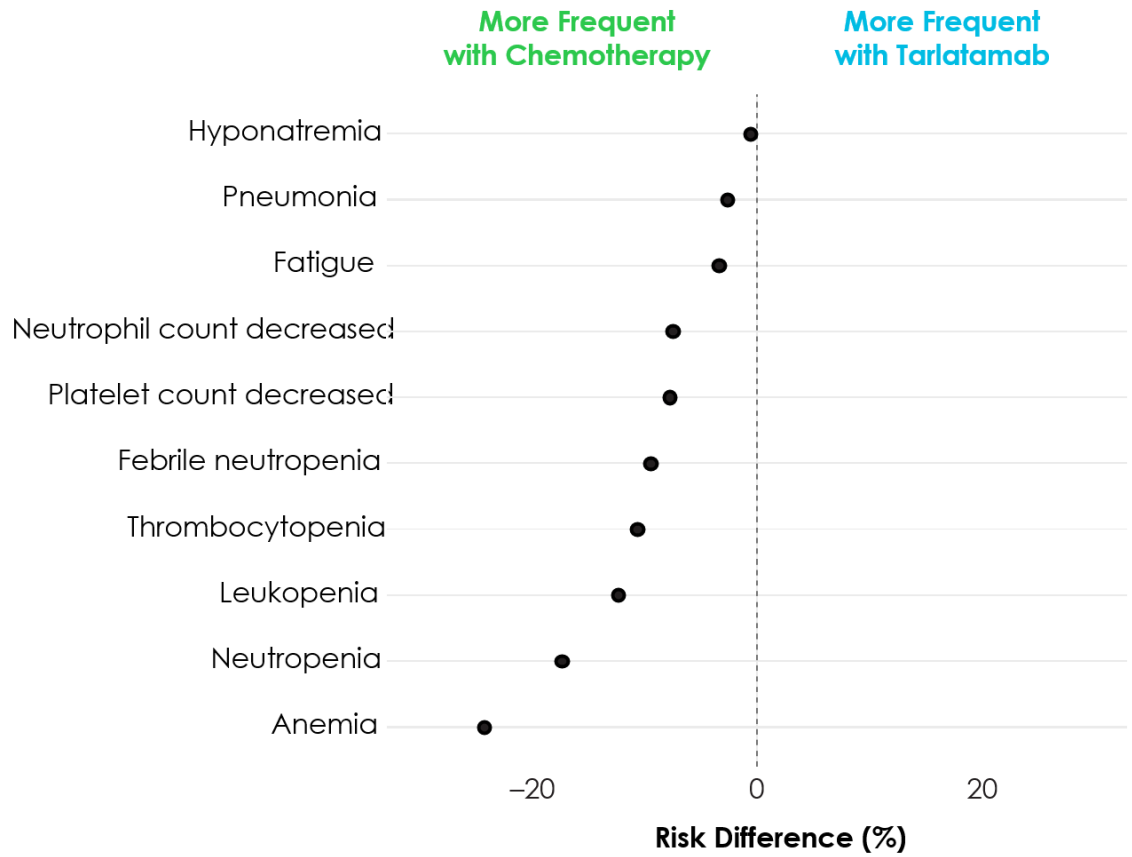
Patients treated with tarlatamab experienced lower incidence of high-grade AEs

Treatment-emergent Adverse Events in > 10% of Patients



Grade ≥ 3 Treatment-emergent Adverse Events in > 5% of Patients



*Adverse events (AEs) shown include adverse events of interest for tarlatamab and selected known adverse events for chemotherapy.

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Conclusions

In the phase 3 DeLLphi-304 randomized controlled trial evaluating tarlatamab versus chemotherapy in patients with SCLC whose disease had progressed or recurred following one line of platinum-based chemotherapy with or without immune-checkpoint inhibitor:

- 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 adverse events and a lower incidence of adverse events that led to treatment discontinuations
- CRS and ICANS were mostly grade 1 or 2 in severity and generally manageable

- **THE SUPERIOR SURVIVAL OUTCOMES COUPLED WITH THE FAVORABLE PATIENT-REPORTED OUTCOMES 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**

2L, second line; **CRS**, cytokine release syndrome; **ICANS**, immune effector cell-associated neurotoxicity syndrome; **SCLC**, small cell lung cancer.

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