













Small Cell Lung Cancer: New Therapeutic Advances in 2024 October 16, 2024 Taofeek K. Owonikoko, MD, PhD



Disclosures

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- **Research Funding to Institution:** Amgen Inc.; AstraZeneca; Bayer Corporation; Cardiff Oncology, Inc.; Roche/Genentech, Inc.; Merck & Co., Inc.; Novartis Pharmaceuticals Corporation; Y-mAbs Therapeutics, Inc; Daiichi Sankyo; Puma Biosciences; Cyclacel; GSK; Boehringer Ingelheim
- IRC/DSMB: EMD Serono, Roche/Genentech
- Co-founder or Stock Ownership: Cambium Oncology; Taobob LLC/Coherus Biosciences; GenCART;

Paradigm or practice change in SCLC

Therapeutic Advances in SCLC: Yes (/) or No (X)?

Years	LS-SCLC Frontline induction	LS-SCLC Maintenance/ Consolidation	ES-SCLC Frontline induction	ES-SCLC Maintenance/ Consolidation	Relapsed SCLC
2019	X	X	✓ Atezolizumab	√Atezolizumab	X
2020	X	X	✓ Durvalumab	√Durvalumab	√Lurbinectedin
2021	X	X	X	X	X
2022	X	X	X	X	X
2023	X	X	X	X	X
2024	X	√Durvalumab	X	√Lurbinectedin	√Tarlatamab





Phase 3 ADRIATIC trial

Ongoing, randomised, double-blind, placebo-controlled, multicentre, international study



At the first interim analysis:1

- Consolidation durvalumab significantly improved the dual primary endpoints of OS and PFS versus placebo; generally consistent treatment benefit across predefined patient subgroups
- Treatment well tolerated; safety consistent with known safety profile of durvalumab in the post-cCRT setting
- Durvalumab + tremelimumab arm remained blinded

BICR, blinded independent central review; cCRT, concurrent chemoradiotherapy; D, durvalumab; LS-SCLC, limited-stage small-cell lung cancer; OS, overall survival; P, placebo; PCI, prophylactic cranial irradiation; PD, progressive disease; PFS, progression-free survival; R, randomisation; RECIST, Response Evaluation Criteria in Solid Tumors; T, tremelimumab; WHO PS, World Health Organization performance status.

 Spigel D, et al. J Clin Oncol 2024;42(17_suppl):LBA5.
 *cCRT and PCI treatment, if received per local standard of care, must have been completed within 1–42 days prior to randomisation. [†]The first 600 patients were randomised in a 1:1:1 ratio to the 3 arms; subsequent patients were randomised 1:1 to either durvalumab or placebo. [‡]PFS assessed by BICR, per RECIST v1.1. University of Maryland Greenebaum Comprehensive Cancer Center

Overall survival (dual primary endpoint)

• Median duration of follow up in censored patients: 37.2 months (range 0.1-60.9)



OS was analyzed using a stratified log-rank test adjusted for receipt of PCI (yes vs no). The significance level for testing OS at this interim analysis was 0.01679 (2-sided) at the overall 4.5% level, allowing for strong alpha control across interim and final analysis timepoints.



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CI, confidence interval; mOS, median OS; NE, not estimable.



Progression-free survival* (dual primary endpoint)

• Median duration of follow up in censored patients: 27.6 months (range 0.0-55.8)



*By BICR per RECIST v1.1.

PFS was analyzed using a stratified log-rank test adjusted for disease stage (I/II vs III) and receipt of PCI (yes vs no). The significance level for testing PFS at this interim analysis was 0.00184 (2-sided) at the 0.5% level, and 0.02805 (2-sided) at the overall 5% level. Statistical significance for PFS was achieved through the recycling multiple testing procedure framework and testing at the 5% (2-sided) alpha level (adjusted for an interim and final analysis).



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mPFS, median PFS. KNOWLEDGE CONQUERS CANCER



Carboplatin and cisplatin CT subgroups – OS

	Carboplatin CT		Cisplatin CT		ITT	
	D (n = 91)	P (n = 88)	D (n = 173)	P (n = 178)	D (n = 264)	P (n = 266)
Median OS (95% CI), months	NR (42.5–NE)	33.4 (21.7–NE)	41.9 (27.7–NE)	34.3 (25.4–40.7)	55.9 (37.3–NE)	33.4 (25.5–39.9)
3-year OS, %	65.3	46.7	52.1	48.1	56.5	47.6
HR (95% CI)	0.56 (0.3	35–0.89)*	0.82 (0.	61–1.10)*	0.73 (0.	57–0.93)†
Multivariable HR (95% CI)	0.55 (0.35–0.87)‡		0.81 (0.60–1.08)‡			-



P, 88 86 84 77 69 63 57 52 47 45 41 28 22 16 11 8 6 3 1 1 0 0 carboplatin



*Subgroup HRs and CIs calculated using an unstratified Cox proportional hazards model. †ITT HR and CIs calculated using a Cox proportional hazards model stratified by receipt of PCI. ‡Multivariable analysis interaction p-value 0.17.

University of Maryland Greenebaum Comprehensive Cancer Center

Senan S et al. ESMO 2024 (abstr LBA81)



Carboplatin and cisplatin CT subgroups – PFS

	Carboplatin CT		Cisplatin CT		ITT		
	D (n = 91)	P (n = 88)	D (n = 173)	P (n = 178)	D (n = 264)	P (n = 266)	
Median PFS (95% CI), months	27.9 (11.1–38.7)	9.2 (5.8–14.6)	11.4 (9.0–23.4)	9.7 (7.4–13.3)	16.6 (10.2–28.2)	9.2 (7.4–12.9)	
2-year PFS, %	54.8	33.2	41.8	34.8	46.2	34.2	
HR (95% CI)	0.61 (0.4	1–0.90)*	0.86 (0.6	5–1.13)*	0.76 (0.6	61–0.95)†	
Multivariable HR (95% CI)	0.60 (0.40–0.88)‡		0.89 (0.67–1.17)‡		-	_	





*Subgroup HRs and CIs calculated using an unstratified Cox proportional hazards model. †ITT HR and CIs calculated using a Cox proportional hazards model stratified by TNM stage and receipt of PCI. ‡Multivariable analysis interaction p-value 0.11.

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BID and QD RT subgroups – OS

	BID RT		QD RT		ITT	
	D (n = 69)	P (n = 79)	D (n = 195)	P (n = 187)	D (n = 264)	P (n = 266)
Median OS (95% CI), months	NR (NE–NE)	44.8 (29.4–NE)	41.9 (32.0–NE)	26.1 (21.7–36.8)	55.9 (37.3–NE)	33.4 (25.5–39.9)
3-year OS, %	65.8	57.4	53.1	43.3	56.5	47.6
HR (95% CI)	0.68 (0.4	40–1.14)*	0.72 (0.5	55–0.96)*	0.73 (0.	57–0.93) [†]
Multivariable HR (95% CI)	0.71 (0.42–1.18)‡		0.73 (0.55–0.96)‡			-





*Subgroup HRs and CIs calculated using an unstratified Cox proportional hazards model. †ITT HR and CIs calculated using a Cox proportional hazards model stratified by receipt of PCI. ‡Multivariable analysis interaction p-value 0.95.

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BID and QD RT subgroups – PFS

	BID RT		QD RT		ITT	
	D (n = 69)	P (n = 79)	D (n = 195)	P (n = 187)	D (n = 264)	P (n = 266)
Median PFS (95% CI), months	38.7 (22.7–NE)	14.3 (9.1–28.1)	11.4 (9.0–19.5)	7.8 (6.4–11.5)	16.6 (10.2–28.2)	9.2 (7.4–12.9)
2-year PFS, %	60.5	42.9	41.0	30.3	46.2	34.2
HR (95% CI)	0.72 (0.4	5–1.13)*	0.77 (0.6	0–1.00)*	0.76 (0	.61–0.95)†
Multivariable HR (95% CI)	0.73 (0.46–1.14)‡		0.79 (0.61–1.03)‡		_	





*Subgroup HRs and CIs calculated using an unstratified Cox proportional hazards model. †ITT HR and CIs calculated using a Cox proportional hazards model stratified by TNM stage and receipt of PCI. ‡Multivariable analysis interaction p-value 0.75.

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PCI-yes and PCI-no subgroups – OS

	PCI-yes		PCI-no		ITT	
	D (n = 142)	P (n = 143)	D (n = 122)	P (n = 123)	D (n = 264)	P (n = 266)
Median OS (95% CI), months	NR (43.9–NE)	42.5 (33.4–NE)	37.3 (24.3–NE)	24.1 (18.8–31.1)	55.9 (37.3–NE)	33.4 (25.5–39.9)
3-year OS, %	62.1	56.5	50.2	37.3	56.5	47.6
HR (95% CI)	0.75 (0.5	52–1.07)*	0.71 (0.5	51–0.99)*	0.73 (0.	57–0.93)†
Multivariable HR (95% CI)	0.72 (0.5	50–1.03)‡	0.73 (0.5	52–1.02) [‡]		-





*Subgroup HRs and CIs calculated using an unstratified Cox proportional hazards model. †ITT HR and CIs calculated using a Cox proportional hazards model stratified by receipt of PCI. ‡Multivariable analysis interaction p-value 0.96.

CI, confidence interval; NE, not estimable; NR, not reached; yr, year.

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PCI-yes and PCI-no subgroups – PFS

	PCI-yes		PCI	PCI-no		ITT		
	D (n = 142)	P (n = 143)	D (n = 122)	P (n = 123)	D (n = 264)	P (n = 266)		
Median PFS (95% CI), months	28.2 (16.8–44.2)	13.0 (9.2–17.0)	9.1 (7.3–14.3)	7.4 (5.7–9.2)	16.6 (10.2–28.	2) 9.2 (7.4–12.9)		
2-year PFS, %	54.6	38.5	37.1	29.3	46.2	34.2		
HR (95% CI)	0.73 (0.5	2–1.00)*	0.80 (0.5	9–1.09)*	0.7	6 (0.61–0.95) [†]		
Multivariable HR (95% CI)	0.72 (0.52–0.99)‡		0.84 (0.61–1.15)‡			_		





*Subgroup HRs and CIs calculated using an unstratified Cox proportional hazards model. †ITT HR and CIs calculated using a Cox proportional hazards model stratified by TNM stage and receipt of PCI. ‡Multivariable analysis interaction p-value 0.50.

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TNM, Tumour-Node-Metastasis.

Senan S et al. ESMO 2024 (abstr LBA81)



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Concurrent Chemoradiation +/- Atezolizumab (atezo) in limited-stage small cell lung cancer (LS-SCLC): Results of NRG Oncology/Alliance LU005

Kristin A. Higgins, Chen Hu, Helen J. Ross, Salma K. Jabbour, David E. Kozono, Taofeek K. Owonikoko, Kyoichi Kaira, Amit K. Gupta, Pranshu Mohindra, Elie G. Dib, Jeremy Brownstein, Stephen Chun, Charles S. Kuzma, Rupesh R. Kotecha, Adedayo A. Onitilo, Yuhchyau Chen, Tom Stinchcombe, Xiaofei F. Wang, Rebecca Paulus, Jeffrey D. Bradley



ASTRO 2024 September 30, 2024



NRG LU005 Schema

Phase III (N = 544; US & Japanese sites)

NCT03811002



[#]Thoracic RT 45 Gy BID (1.5 Gy x 30 fractions ->3 weeks) or 66 Gy daily (2 Gy x 33 fractions ->6.5 weeks) beginning with cycle 2 of chemotherapy; *cisplatin (preferred) or carboplatin; first cycle of chemotherapy given prior to study entry, 3 given on study (for a total of 4 cycles); **All patients with a CR or near CR are strongly recommended to receive prophylactic cranial irradiation (PCI; 25 Gy)



Overall Survival





Hazard ratio and one-sided p-value stratified by RT schedule, chemotherapy, and sex

Progression Free Survival



Months Since Randomization



Hazard ratio and p-value stratified by RT schedule, chemotherapy, and sex

Basic construct and mechanism of antitumor efficacy



Rudin C et al. J Hematol Oncol. 2023; 16: 66.



#WCLC24

Tarlatamab Sustained Clinical Benefit and Safety in Previously Treated SCLC: DeLLphi-301 Phase 2 Extended Follow-Up

Jacob Sands,¹ Byoung Chul Cho, Myung-Ju Ahn, Martin Reck, Jean Bustamante Alvarez, Horst-Dieter Hummel, Hiroaki Akamatsu, Melissa L. Johnson, Enriqueta Felip, Sabin Handzhiev, Ippokratis Korantzis, Hiroki Izumi, Anne-Marie C. Dingemans, Fiona Blackhall, Taofeek K. Owonikoko, Jürgen Wolf, Suresh S. Ramalingam, Hossein Borghaei, Shuang Huang, Tony Jiang, Erik S. Anderson, Pablo Martinez, Ali Hamidi, Sujoy Mukherjee, Luis Paz-Ares

¹Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

DeLLphi-301 Study Design

• Phase 2, open-label study (NCT05060016)



Primary Endpoint: ORR per RECIST 1.1 by BICR

Secondary Endpoints Included: DOR, DCR, PFS per RECIST 1.1 by BICR, OS, TEAEs, tarlatamab serum concentrations

Data cutoff was January 12, 2024 for all efficacy and safety outcomes, except for OS. For OS, the data cutoff was May 16, 2024 to obtain mature OS data with a median follow-up of 20.7 months. *Once 30 patients per dose level had the opportunity to confirm an objective response after the first post-treatment scan or \geq 13 weeks of follow-up, whichever occurred first. BICR, blinded independent central review; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intention-to-treat; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q2W, every 2 weeks; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; SCLC, small cell lung cancer; TEAE, treatment-emergent adverse event.

#WCLC24 clc2024.iaslc.org

Sustained Disease Control*



- Tumor shrinkage was seen in 72% of patients
- The median duration of disease control was 6.9 months (95% CI, 5.4–8.6)

26 patients (26%; 3 CR, 20 PR, 3 SD) had sustained disease control ≥ 52 weeks

Data cutoff, January 12, 2024. The efficacy analysis set consists of patients in Parts 1 and 2 (N = 100). One patient did not receive tarlatamab 10 mg but was included in the ITT analysis. Part 3 was a safety substudy and was not included in this response analysis. *Sustained disease control was defined as disease control (CR, PR, or SD) with time on treatment \geq 52 weeks.

BOR, best overall response; CR, complete response; ITT, intention-to-treat; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

#WCLC24 vclc2024.iaslc.org

Progression-Free Survival



• Median PFS was 4.3 months (95% CI, 2.9–5.6)

Data cutoff, January 12, 2024. Median follow-up for PFS was 16.4 months. The efficacy analysis set consists of patients in Parts 1 and 2 (N = 100). One patient did not receive tarlatamab 10 mg but was included in the ITT analysis. Part 3 was a safety substudy and was not included in this response analysis. ITT, intention-to-treat; **PFS**, progression-free survival.

Overall Survival

#WCLC24 clc2024.iaslc.org



Median OS was 15.2 months (95% CI, 10.8–NE)

Median follow-up for OS was 20.7 months. Data cutoff, May 16, 2024. The efficacy analysis set consists of patients in Parts 1 and 2 (N = 100). One patient did not receive tarlatamab 10 mg but was included in ITT analysis. Part 3 was a safety substudy and was not included in this response analysis. *95% CI, 63.2–81.2. [†]95% CI, 46.3–66.3. [‡]95% CI, 35.6–55.8. Progression-free interval after first line platinum treatment is defined as days from the last first line platinum treatment to disease progression or start of second line treatment, whichever is earlier. **ITT**, intention-to-treat; **NE**, not estimable; **OS**, overall survival.

Overall Survival

#WCLC24 clc2024.iaslc.org



OS was similar regardless of progression-free interval after 1L platinum treatment (< 90 d vs ≥ 90 d)

Median follow-up for OS was 20.7 months. Data cutoff, May 16, 2024. The efficacy analysis set consists of patients in Parts 1 and 2 (N = 100). One patient did not receive tarlatamab 10 mg but was included in ITT analysis. Part 3 was a safety substudy and was not included in this response analysis. *95% CI, 63.2–81.2. [†]95% CI, 46.3–66.3. [‡]95% CI, 35.6–55.8. Progression-free interval after first line platinum treatment is defined as days from the last first line platinum treatment to disease progression or start of second line treatment, whichever is earlier. **ITT**, intention-to-treat; **NE**, not estimable; **OS**, overall survival.

T-Cell engagers in clinical development



Rudin C et al. J Hematol Oncol. 2023; 16: 66; Mikami H et al. Cancer Immunol Res (2024) 12 (6): 719–730.

Maintenance treatment



Owonikoko TK et al. Journal of Clinical Oncology, Volume 39, Number 12





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Tarlatamab with a PD-L1 Inhibitor as First-Line Maintenance After Chemo-Immunotherapy for ES-SCLC: DeLLphi-303 Phase 1b Study

<u>Sally C. M. Lau</u>¹, Myung-Ju Ahn, Mor Moskovitz, Michael Pogorzelski, Simon Haefliger, Kelly G. Paulson, Amanda Parkes, Yuyang Zhang, Ali Hamidi, Martin Wermke

Department of Medicine, Perlmutter Cancer Center; NYU Grossman School of Medicine; New York, NY, USA UNIVERSITY of MARYLAND MARLENE AND STEWART GREENEBAUM COMPREHENSIVE CANCER CENTER

DeLLphi-303: Tarlatamab with PD-L1 Inhibitor as 1LM

• Phase 1b, multicenter, open-label study (NCT05361395)

1L Chemo-IO

Platinum-etoposide + anti-PD-L1 therapy (4-6 cycles)	 Enrollment Key Inclusion Criteria No disease progression following 4-6 cycles of platinum-etoposide + PD-L1 inhibitor Eligible if no access to 1L PD-L1 inhibitor Prior treatment for LS-SCLC permitted ECOG PS 0-1 Treated and asymptomatic brain metastases allowed 	Non- randomized Switching to different PD- L1 inhibitor permitted	Tarlatamab (10 mg IV Q2W) + Atezolizumab (1680 mg IV Q4W) Tarlatamab (10 mg IV Q2W) + Durvalumab (1500 mg IV Q4W)
	allowedDLL3 positivity not required	permitted	Durvaluman (1900 mg iv Q4w)

- Must initiate C1D1 of maintenance phase within 8 weeks of the start of the last cycle of 1L chemo-immunotherapy
- Median follow-up time (N = 88): 10.0 months (range: 1.4–20.4)

Primary Endpoints*: Dose-limiting toxicities, treatment-emergent / treatment-related adverse events (TEAEs, TRAEs) **Secondary Endpoints**[†]: Disease control and PFS per local RECIST v1.1 assessment, OS

Data cutoff was May 31, 2024. *Also includes vital signs, electrocardiograms, and clinical laboratory tests. [†]Also includes objective response, duration of response, serum concentrations of tarlatamab, quantification of biomarker expression, and incidence of anti-tarlatamab antibody formation. **1L**, first-line; **1LM**, first-line maintenance; **C1D1**, cycle 1 day 1; **DLL3**, delta-like ligand 3; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **ES**, extensive-stage; **IO**, immuno-oncology agent; **IV**, intravenous; **LS**, limited-stage; **PD-L1**, programmed death-ligand 1; **Q2W**, once every two weeks; **Q4W**, once every four weeks; **RECIST**, response evaluation criteria in solid tumors; **SCLC**, small cell lung cancer.

University of Maryland Greenebaum Comprehensive Cancer Center

1L Maintenance

DCR and duration of disease control, beginning from 1L maintenance

Given study eligibility required non-PD to 1L chemo +/- IO, DCR and mDoDC were favored over ORR and mDOR in assessing clinical benefit.

Tarlatamab + Atezolizumab

- DCR: 30/48 = 62.5% (95% CI: 47.4-76.0)
- Median duration of DC = 7.2 months (95% CI: 5.6, NE)

Tarlatamab + Durvalumab, n = 25

- DCR: 25/40 = 62.5% (95% CI: 45.8, 77.3)
- Median duration of DC = NE (95% CI: 3.9, NE)



• Tarlatamab with a PD-L1 inhibitor as 1LM demonstrated sustained disease control

• For tarlatamab + PD-L1 inhibitor, DCR was 62.5% (95% CI: 51.5–72.6) and mDoDC was 9.3 months (95% CI: 5.6, NE)

1L, first-line; 1LM, first-line maintenance; CI, confidence interval; DC, disease control; DCR, disease control rate; IO, immuno-oncology agent; mDoDC, median duration of disease control; mDOR, median duration of response; NE, not estimable; ORR, objective response rate; PD, progressive disease; PD-L1, programmed cell death ligand-1; Q4W, once every four weeks.

PFS, beginning from 1L maintenance



After a median time from 1L chemoimmunotherapy to 1LM of 3.6 months, tarlatamab with a PD-L1 inhibitor as 1LM showed promising PFS, with mPFS of 5.6 months.

1L, first-line; 1LM, first-line maintenance; CI, confidence interval; IO, immuno-oncology agent; NE, not estimable; PD-L1, programmed death-ligand 1; PFS, progression-free survival.

OS, beginning from 1L maintenance



After a median time from 1L chemoimmunotherapy to 1LM of 3.6 months, tarlatamab with a PD-L1 inhibitor as 1LM showed a 9-month OS of 89%.

1L, first-line; 1LM, first-line maintenance; CI, confidence interval; IO, immuno-oncology agent; OS, overall survival.

mFORTE Trial:

ECOG PS

Ongoing

cycles of

Adequate

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IMforte Trial: Maintenance With Lurbinectedin Plus Atezolizumab Shows OS, PFS Benefit in ES-SCLC

By Cecilia Brown - Last Updated: October 17, 2024



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Conclusions

- Major changes in the treatment of SCLC witnessed in 2024
- ADRIATIC trial established a role for durvalumab as consolidation post chemorad in LS-SCLC
- ImFORTE trial also demonstrated clinical benefit and a new paradigm of maintenance therapy with a cytotoxic agent in ES-SCLC
- Tarlatamab offers both a new option and a new treatment paradigm for BiTE as salvage therapy in relapsed SCLC

