Updated treatment strategies in SCLC

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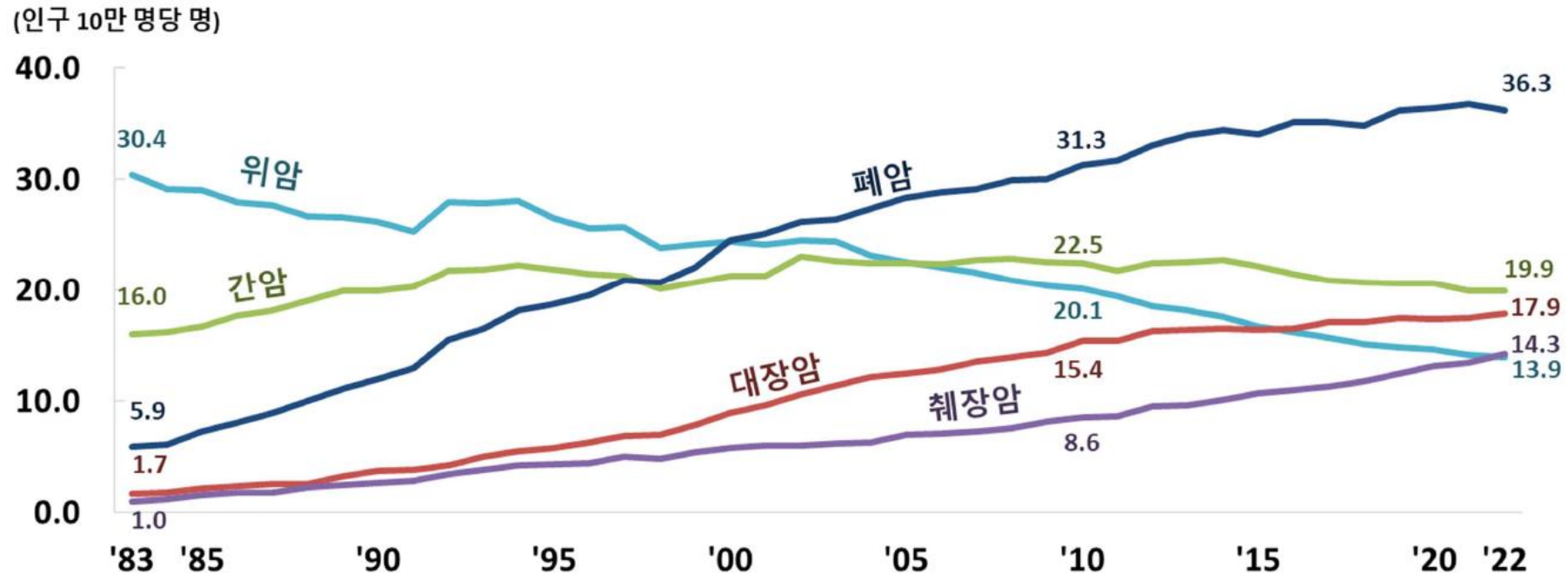
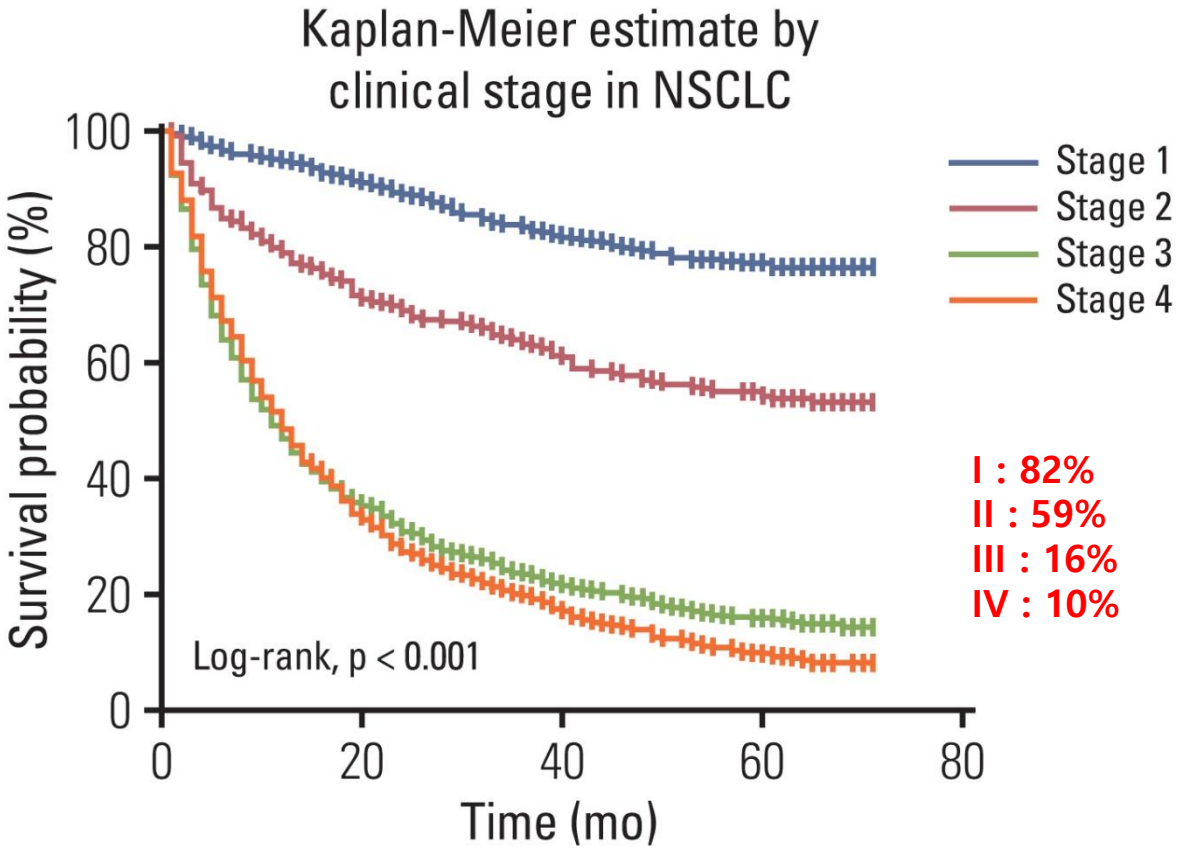
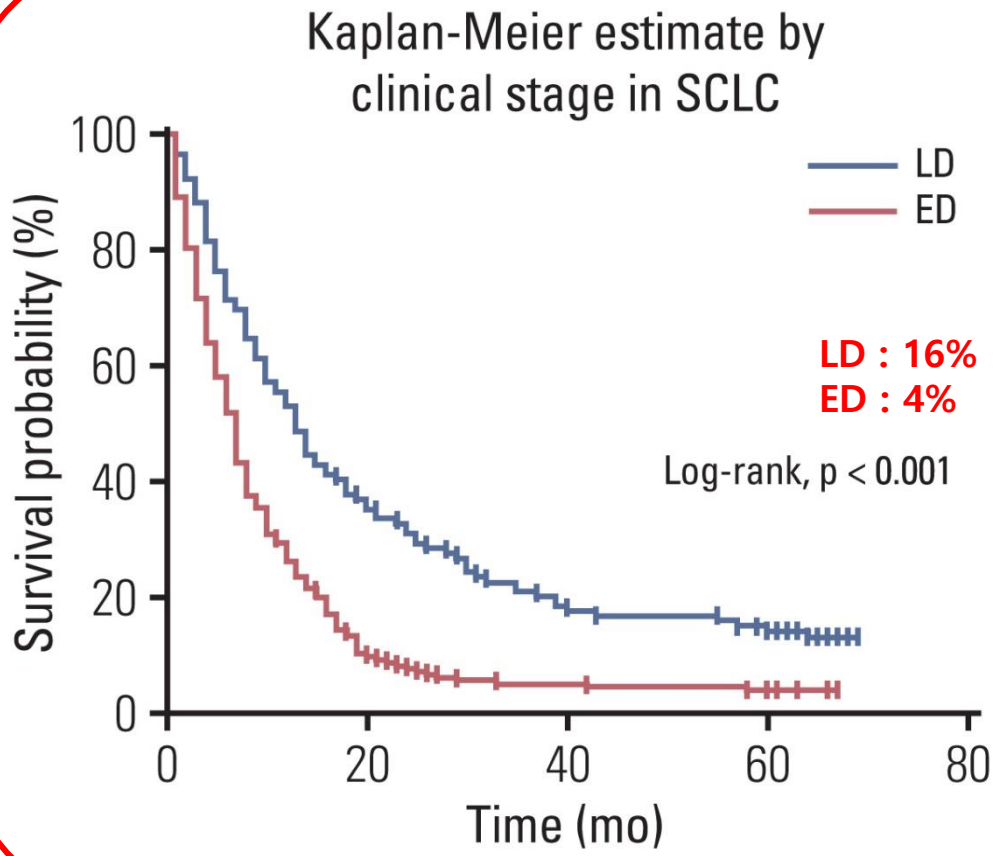
Cancer mortality rate trends (1983-2022)



30대는 위암, 40대는 유방암, 50대는 간암, 60세 이상은 폐암 사망률이 가장 높음

5-Year Survival Rate

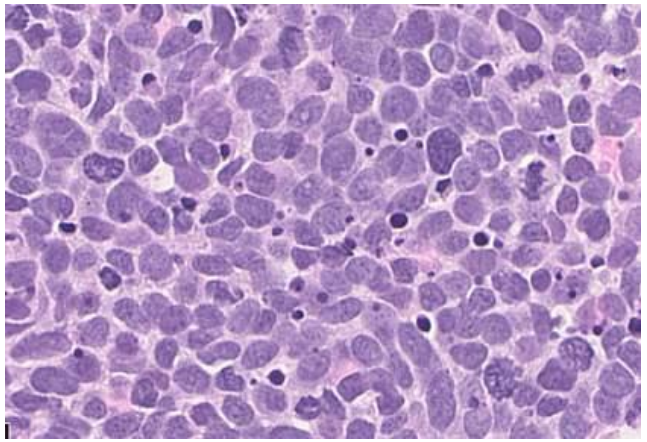




Five-Year Overall Survival and Prognostic Factors in Patients with Lung Cancer: Results from the Korean Association of Lung Cancer Registry (KALC-R) 2015

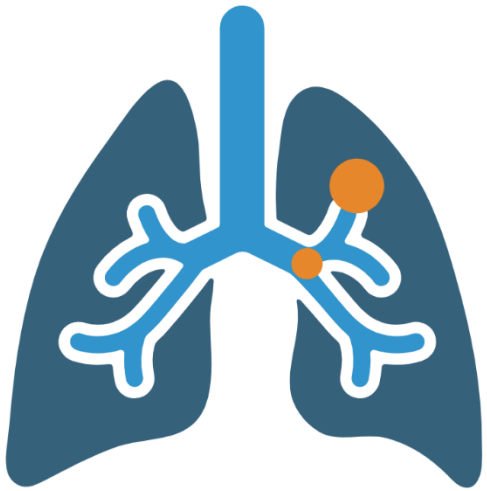
Small cell lung cancer

- A fast-growing, aggressive type of lung cancer that originates in neuroendocrine cells of the lungs.
- **Epidemiology:** Accounts for **10-15%** of all lung cancers.
- Characteristics:
  - Strongly associated with **smoking** (>95% of cases).
  - Rapid growth and early metastasis.
  - Often diagnosed at an **advanced stage**.
- **Poor prognosis** due to early spread.



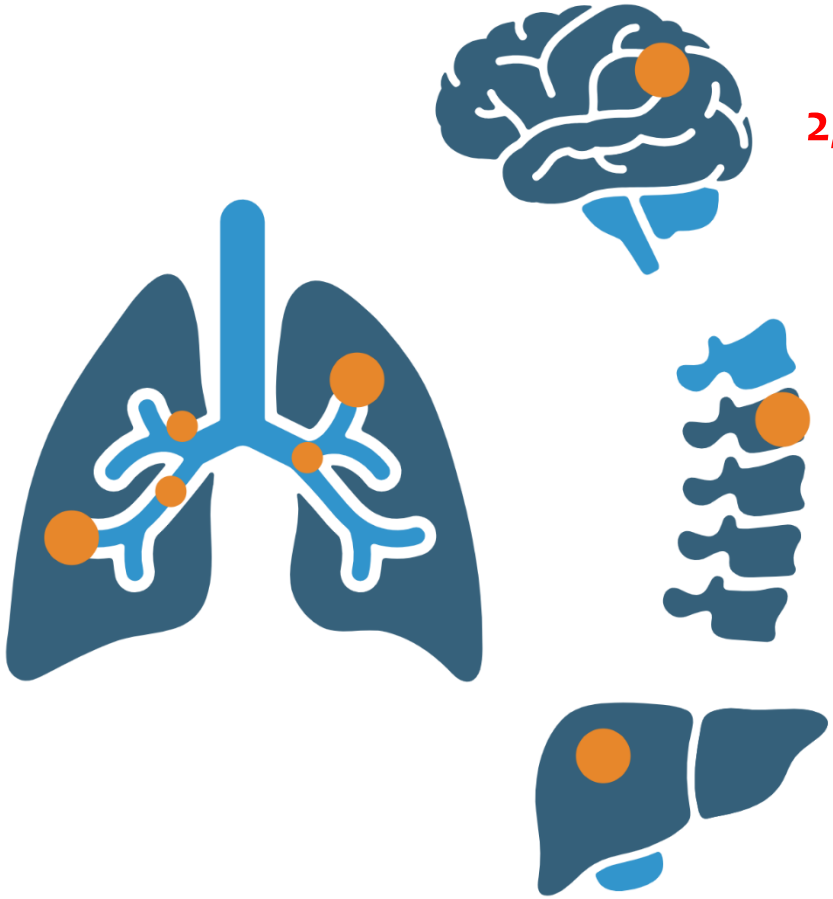
Diagnosis and Stage

1/3 at Diagnosis



Limited Stage

2/3 at Diagnosis



Extensive Stage

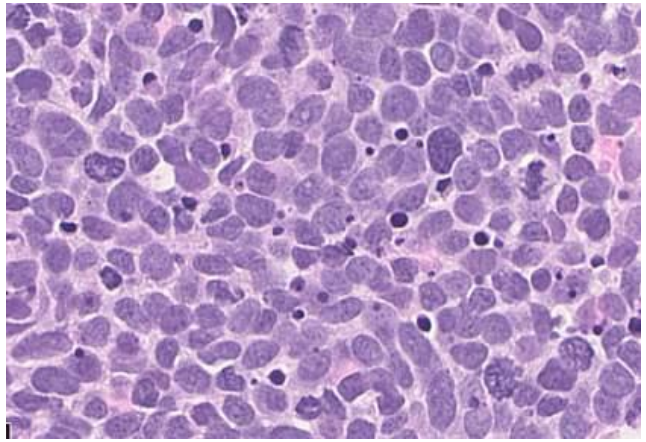
Stage and Treatment of lung cancer

Non-small cell lung cancer

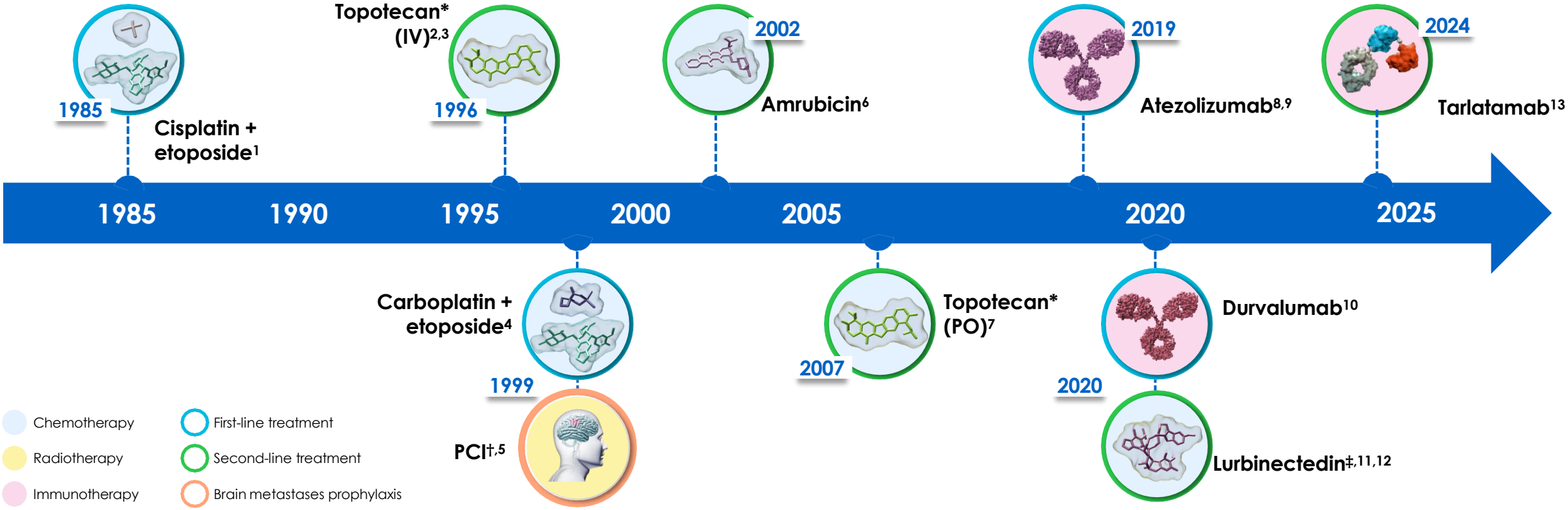
	Treatment plan
Stage IA	Surgery
Stage IB-II	Surgery ± Adjuvant CTx Surgery ± Adjuvant Target therapy Neoadjuvant IO + CTx -> Surgery
Stage IIIA/IIIB	Surgery ± Adjuvant CTx ± Adjuvant IO Tx Surgery ± Adjuvant Target therapy Neoadjuvant IO + CTx -> Surgery ± Adjuvant IO Tx Concurrent chemoradiation ± Operation or Consolidation ImmunoTx
Stage IIIB/C	
Stage IV or Recurred dz	Targeted therapy Immunotherapy ± CTx Cytotoxic CTx Supportive care

Small cell lung cancer

	Treatment plan
Limited stage	Concurrent CCRTx followed by PCI
Extensive stage	Immunotherapy ± CTx Cytotoxic CTx



Timeline of SCLC



Timeline depicts SOC and new therapies for SCLC approved by the FDA.

*Relapsed SCLC[2,7]. †12% of patients treated with PCI had extensive initial disease[10]. ‡Metastatic SCLC[12,13].

ES-SCLC, extensive-stage SCLC; **FDA**, Food and Drug Administration; **IV**, intravenous; **PCI**, prophylactic cranial irradiation; **PO**, oral; **SCLC**, small cell lung cancer; **SOC**, standard of care.

1. Evans WK, et al. *J Clin Oncol*. 1985;3:1471-1477. 2. TOPOTECAN Injection Prescribing Information, Pfizer; 2014. 3. Ardizzoni A, et al. *J Clin Oncol*. 1997;15:2090-2096. 4. Okamoto H, et al. *J Clin Oncol*. 1999;17:3540-3545. 5. Aupérin A, et al. *N Engl J Med*. 1999;341:476-484. 6. von Pawel J, et al. *J Clin Oncol*. 2014;32:4012-4019. 7. HYCAMTIN® (topotecan) Prescribing Information, GlaxoSmithKline;2007. 8. FDA. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-atezolizumab-extensive-stage-small-cell-lung-cancer. Accessed May 15, 2024. 9. Horn L, et al. *N Engl J Med*. 2018;379:2220- 2229. 10. FDA. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-durvalumab-extensive-stage-small-cell-lung-cancer. Accessed May 15, 2024. 11. Trigo J, et al. *Lancet Oncol*. 2020;21:645-654. 12. FDA. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-lurbinectedin-metastatic-small-cell-lung-cancer . Accessed May 15, 2024.
13. FDA. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-tarlatamab-dlle-extensive-stage-small-cell-lung-cancer#:~:text=On%20May%2016%2C%202024%2C%20the,Imdelltra%2C%20Amgen%2C%20Inc.). Accessed July 9, 2024.

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Treatment of SCLC

Limited disease	Concurrent CTx(Etoposide + platinum) + RTx followed by PCI

The NEW ENGLAND JOURNAL of MEDICINE

Durvalumab in Limited-Stage Small-Cell Lung Cancer

A PLAIN LANGUAGE SUMMARY

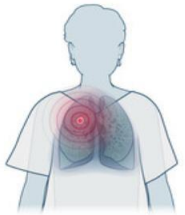
Based on the NEJM publication: Durvalumab after Chemoradiotherapy in Limited-Stage Small-Cell Lung Cancer by Y. Cheng et al. (published September 13, 2024)

In this trial, researchers assessed whether adjuvant therapy with durvalumab would prolong survival among patients with limited-stage small-cell lung cancer who did not have disease progression after concurrent chemoradiotherapy.

Small-cell lung cancer is an aggressive cancer that accounts for approximately 15% of all lung tumors; approximately one third of patients present with limited-stage disease.

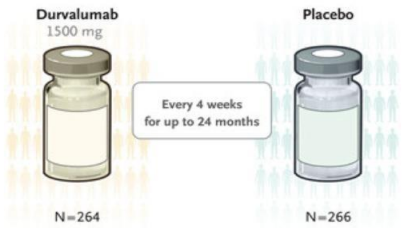
WHY WAS THE TRIAL DONE?

Most patients treated for limited-stage small-cell lung cancer have disease relapse within 2 years after starting treatment, and 5-year overall survival ranges from 29 to 34%. No advances in systemic treatments have been made in the past three decades.



HOW WAS THE TRIAL CONDUCTED?

530 patients with limited-stage small-cell lung cancer who did not have progression after definitive concurrent chemoradiotherapy were assigned to receive intravenous durvalumab — a selective, high-affinity human IgG1 monoclonal antibody that binds to PD-L1 — or placebo every 4 weeks for up to 24 months. The two primary end points were overall survival and progression-free survival.



PATIENTS

WHO	530 adults
	Median age: 62 years
	Men: 69%; Women: 31%
	Former smokers: 68%; Current smokers: 22%
CLINICAL STATUS	Stage I, II, or III small-cell lung cancer
	Previous concurrent chemoradiotherapy with etoposide plus cisplatin or carboplatin

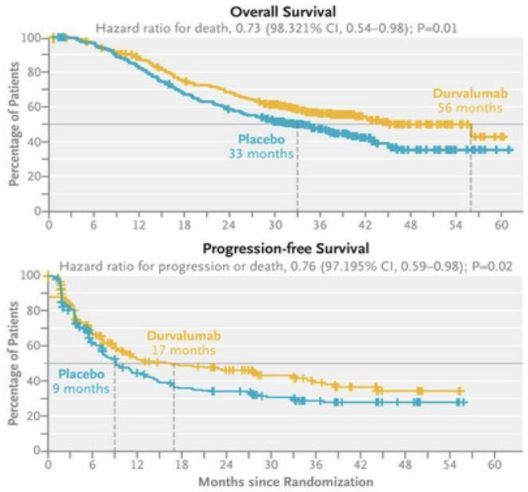
TRIAL DESIGN

- PHASE 3
- ONGOING
- MULTICENTER
- DOUBLE-BLIND
- RANDOMIZED
- PLACEBO-CONTROLLED

RESULTS

In a planned interim analysis, overall survival was significantly longer in the durvalumab group than in the placebo group at a median follow-up of approximately 37 months. Progression-free survival was also significantly longer with durvalumab at a median follow-up of approximately 27 months.

Adverse events with a maximum grade of 3 or 4 occurred in 24% of the patients in each group. Adverse events leading to discontinuation occurred in 16% of the durvalumab recipients and in 11% of the placebo recipients.



LIMITATIONS AND REMAINING QUESTIONS

- Black patients were underrepresented, accounting for only 0.8% of the trial population.
- The trial also assigned 200 patients to receive durvalumab plus tremelimumab, a monoclonal antibody that binds to the cytotoxic T-lymphocyte–associated antigen 4 inhibitory receptor expressed on T cells. Results for that group remain blinded.
- Further studies are warranted on the biologic effects of chemoradiotherapy on subsequent immunotherapy, including effects in different subtypes of small-cell lung cancer.

CONCLUSIONS

Among patients with limited-stage small-cell lung cancer who had not had disease progression after definitive concurrent chemoradiotherapy, adjuvant therapy with durvalumab led to significantly longer overall survival and progression-free survival than placebo.

LINKS: FULL ARTICLE | NEJM QUICK TAKE

FURTHER INFORMATION

Trial registration: ClinicalTrials.gov number, NCT03703297
Trial funding: AstraZeneca
Full citation: Cheng Y, Spigel DR, Cho BC, et al. Durvalumab after chemoradiotherapy in limited-stage small-cell lung cancer. N Engl J Med 2024;391:1313-27. DOI: 10.1056/NEJMoa2404873

2024 ASCO ANNUAL MEETING

ADRIATIC: durvalumab as consolidation treatment for patients with limited-stage small-cell lung cancer (LS-SCLC)

David R. Spigel, Ying Cheng, Byoung Chul Cho, Konstantin Laktionov, Jian Fang, Yuanbin Chen, Yoshitaka Zenke, Ki Hyeong Lee, Qiming Wang, Alejandro Navarro, Reyes Bernabe, Eva Buchmeier, John Wen-Cheng Chang, Isamu Okamoto, Sema Sezgin Goksu, Andrzej Badzio, Bethany Gill, Hema Gowda, Haiyi Jiang, Suresh Senan

PRESENTED BY: Dr David R. Spigel, Sarah Cannon Research Institute, Nashville, TN, USA

ADRIATIC study design

Phase 3, randomized, double-blind, placebo-controlled, multicenter, international study (NCT03703297)

- Stage I–III LS-SCLC (stage I/II inoperable)
- WHO PS 0 or 1
- Had not progressed following cCRT*
- PCI* permitted before randomization

N=730

R‡

Durvalumab
1500 mg Q4W
N=264

Placebo
Q4W
N=266

Durvalumab + tremelimumab
D 1500 mg Q4W + T 75 mg Q4W for 4 doses, followed by D 1500 mg Q4W
N=200

cCRT components
- Four cycles of platinum and etoposide (three permitted†)
- RT: 60–66 Gy QD over 6 weeks or 45 Gy BID over 3 weeks
- RT must commence no later than end of cycle 2 of CT

Stratified by:
Disease stage (I/II vs III)
PCI (yes vs no)

Treatment until investigator-determined progression or intolerable toxicity, or for a **maximum of 24 months**

Dual primary endpoints:
- Durvalumab vs placebo
  - OS
  - PFS (by BICR, per RECIST v1.1)

Key secondary endpoints:
- Durvalumab + tremelimumab vs placebo
  - OS
  - PFS (by BICR, per RECIST v1.1)

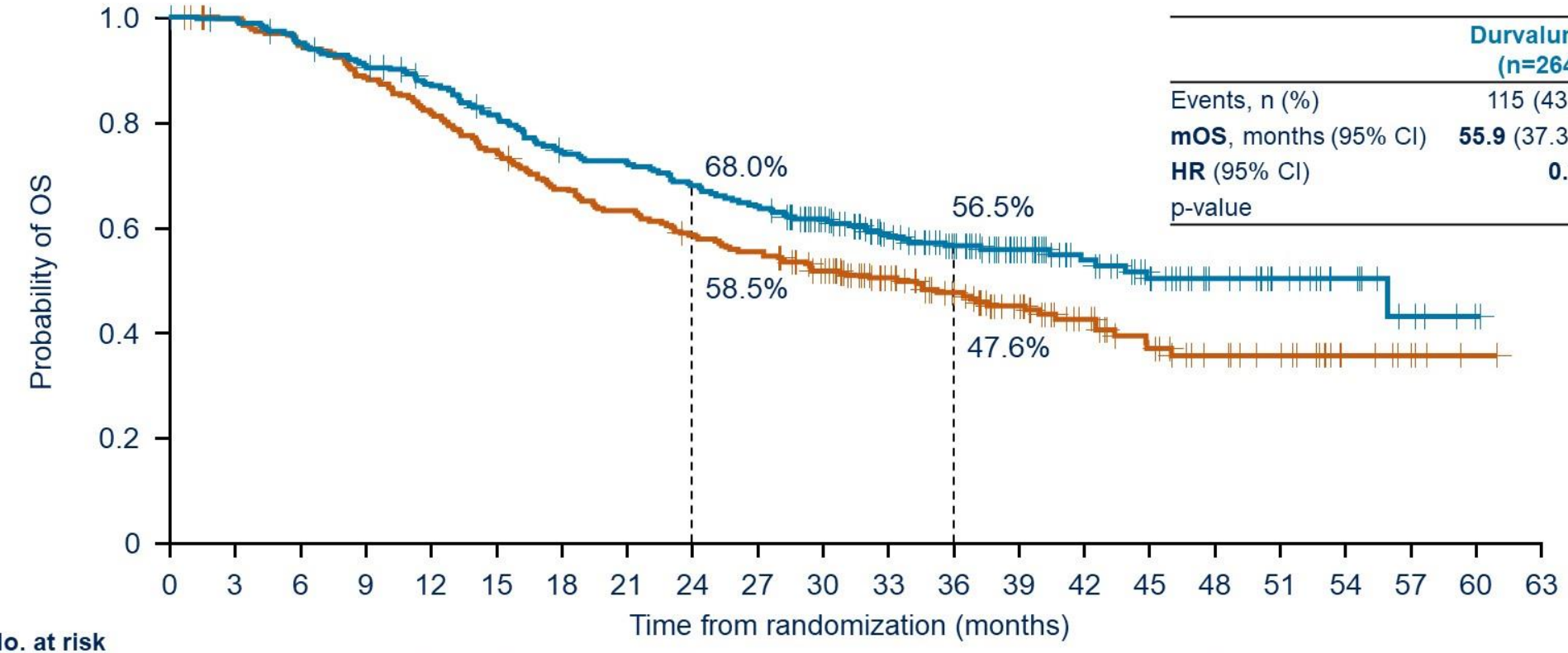
Other secondary endpoints:
- OS/PFS landmarks
- Safety

*cCRT and PCI treatment, if received per local standard of care, must have been completed within 1–42 days prior to randomization.
†If disease control was achieved and no additional benefit was expected with an additional cycle of chemotherapy, in the opinion of the investigator.
‡The first 600 patients were randomized in a 1:1:1 ratio to the 3 treatment arms; subsequent patients were randomized 1:1 to either durvalumab or placebo.

BICR, blinded independent central review; BID, twice daily; CT, chemotherapy; D, durvalumab; PCI, prophylactic cranial irradiation; PS, performance status; Q4W, every 4 weeks; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; RT, radiotherapy; T, tremelimumab; WHO, World Health Organization.

Overall survival (dual primary endpoint)

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



	Durvalumab (n=264)	Placebo (n=266)
Events, n (%)	115 (43.6)	146 (54.9)
mOS, months (95% CI)	**55.9** (37.3–NE)	**33.4** (25.5–39.9)
HR (95% CI)	**0.73** (0.57–0.93)	
p-value	0.0104	

No. at risk																						
Durvalumab	264	261	248	236	223	207	189	183	172	162	141	110	90	68	51	39	27	19	11	5	1	0
Placebo	266	260	247	231	214	195	175	164	151	143	123	97	80	62	44	31	23	19	8	5	1	0

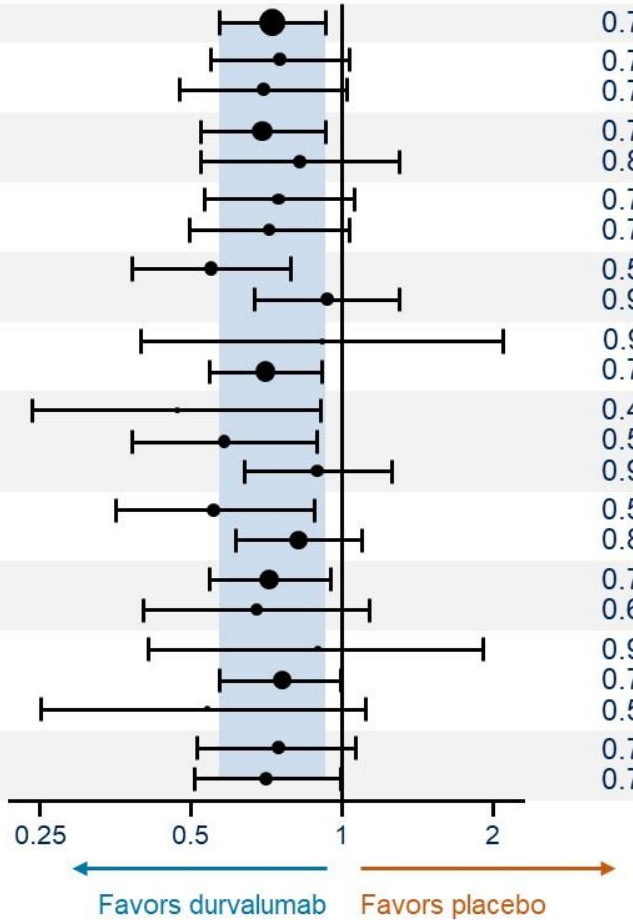
OS was analyzed using a stratified log-rank test adjusted for receipt of PCI (yes vs no). The significance level for testing OS at this interim analysis was 0.01679 (2-sided) at the overall 4.5% level, allowing for strong alpha control across interim and final analysis timepoints.

PRESENTED BY: Dr David R. Spigel

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

OS subgroup analysis

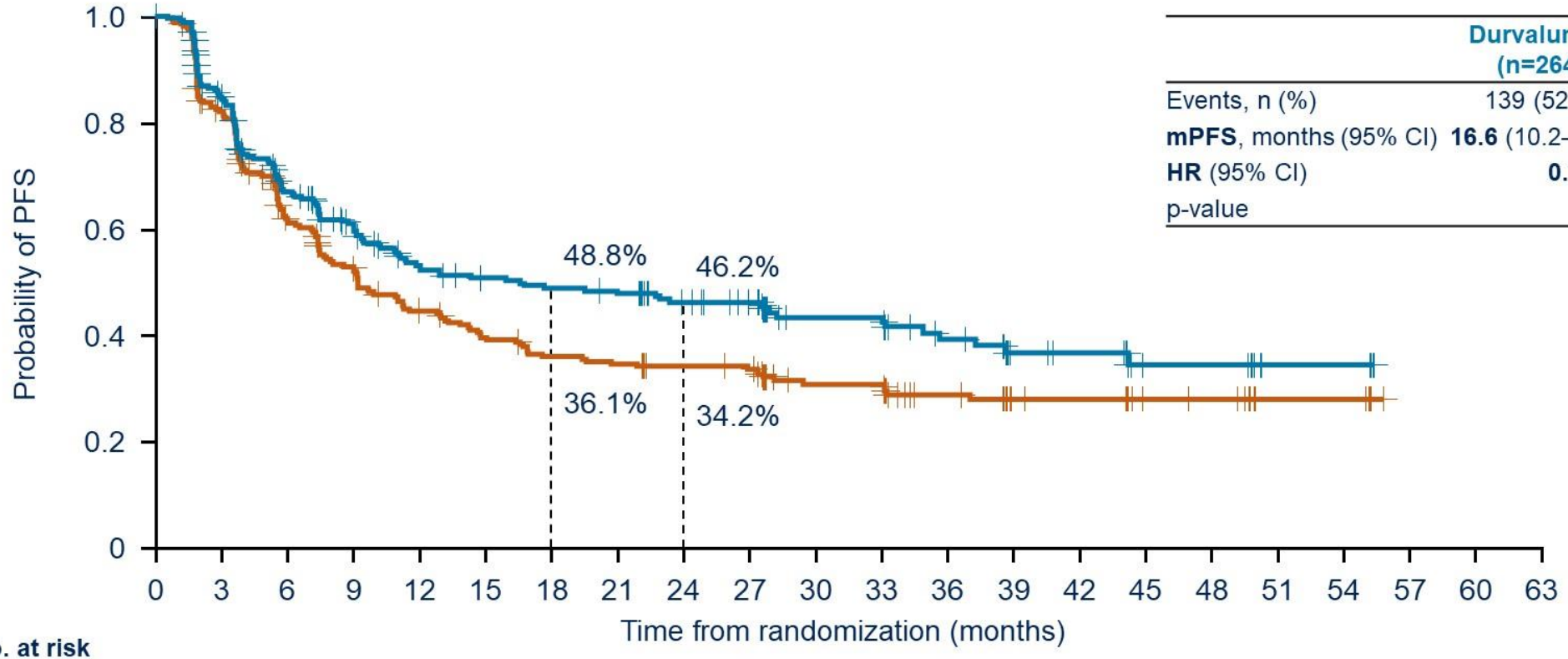
		Events/Patients n/N		HR (95% CI)
		Durvalumab	Placebo	
All patients		115/264	146/266	0.73 (0.57–0.93)
Age	<65 years	69/160	83/162	0.76 (0.55–1.04)
	≥65 years	46/104	63/104	0.70 (0.48–1.02)
Sex	Male	79/178	108/188	0.70 (0.52–0.93)
	Female	36/86	38/78	0.83 (0.52–1.31)
Race	White	60/130	77/137	0.75 (0.53–1.05)
	Asian	53/131	64/121	0.72 (0.50–1.04)
WHO performance status	0	48/133	74/131	0.55 (0.38–0.79)
	1	67/131	72/135	0.94 (0.67–1.31)
AJCC disease stage at diagnosis	I/II	11/33	12/34	0.92 (0.40–2.11)
	III	104/231	134/232	0.71 (0.55–0.91)
Time from end of cCRT* to randomization	<14 days	14/32	24/32	0.47 (0.24–0.91)
	≥14 days to <28 days	37/79	51/80	0.59 (0.38–0.90)
	≥28 days	64/153	71/154	0.90 (0.64–1.27)
Prior chemotherapy regimen	Carboplatin-etoposide	31/ 91	46/88	0.56 (0.35–0.89)
	Cisplatin-etoposide	84/173	100/178	0.82 (0.61–1.10)
Prior radiation schedule	Once daily	92/195	107/187	0.72 (0.55–0.95)
	Twice daily	23/69	39/79	0.68 (0.40–1.14)
Best response to prior cCRT	Complete response	12/31	15/34	0.90 (0.41–1.92)
	Partial response	88/191	116/200	0.76 (0.57–1.00)
	Stable disease	15/42	15/32	0.54 (0.25–1.13)
Prior PCI	Yes	53/142	67/143	0.75 (0.52–1.07)
	No	62/122	79/123	0.71 (0.51–0.99)



*End of chemotherapy or radiotherapy, whichever was latest.
Intention-to-treat analysis stratified, subgroup analyses unstratified. Not all prespecified subgroups are included in the plot.
Size of circle is proportional to number of events across both arms.

Progression-free survival* (dual primary endpoint)

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



	Durvalumab (n=264)	Placebo (n=266)
Events, n (%)	139 (52.7)	169 (63.5)
mPFS, months (95% CI)	**16.6** (10.2–28.2)	**9.2** (7.4–12.9)
HR (95% CI)	**0.76** (0.61–0.95)	
p-value	0.0161	

No. at risk																						
Durvalumab	264	212	161	135	113	105	101	98	84	78	51	51	33	21	19	10	10	4	4	0	0	0
Placebo	266	208	146	122	100	88	79	76	71	69	47	47	34	23	22	15	14	5	5	0	0	0

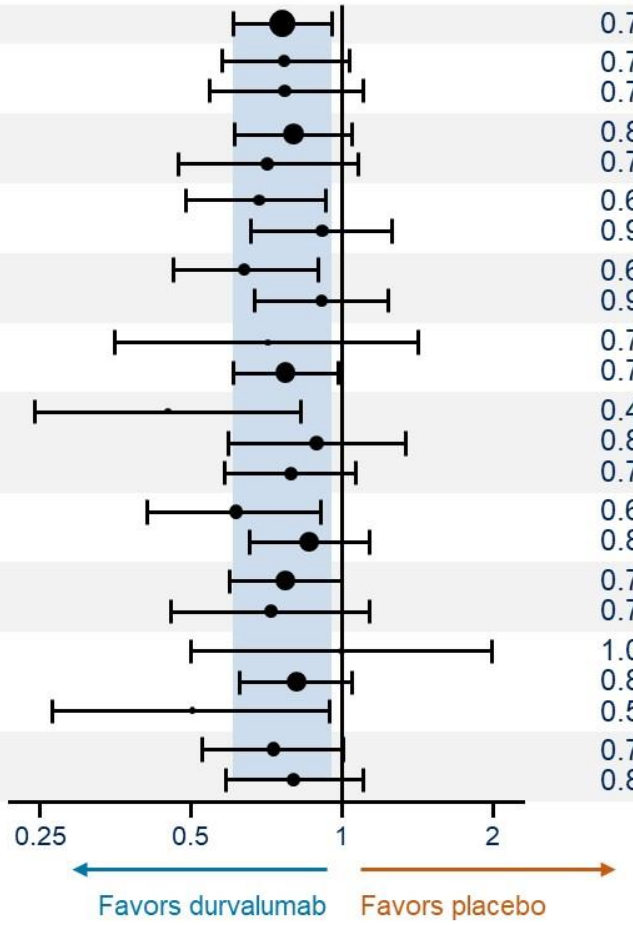
*By BICR per RECIST v1.1.

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).

mPFS, median PFS.

PFS subgroup analysis

		Events/Patients n/N		HR (95% CI)
		Durvalumab	Placebo	
All patients		139/264	169/266	0.76 (0.61–0.95)
Age	<65 years	83/160	98/162	0.77 (0.58–1.03)
	≥65 years	56/104	71/104	0.77 (0.54–1.10)
Sex	Male	96/178	120/188	0.80 (0.61–1.04)
	Female	43/86	49/78	0.71 (0.47–1.08)
Race	White	65/130	90/137	0.68 (0.49–0.93)
	Asian	72/131	75/121	0.91 (0.66–1.26)
WHO performance status	0	60/133	82/131	0.64 (0.46–0.90)
	1	79/131	87/135	0.91 (0.67–1.24)
AJCC disease stage at diagnosis	I/II	14/33	19/34	0.71 (0.35–1.42)
	III	125/231	150/232	0.77 (0.61–0.98)
Time from end of cCRT* to randomization	<14 days	18/32	27/32	0.45 (0.24–0.83)
	≥14 days to <28 days	43/79	50/80	0.89 (0.59–1.34)
	≥28 days	78/153	92/154	0.79 (0.58–1.07)
Prior chemotherapy regimen	Carboplatin-etoposide	44/91	57/88	0.61 (0.41–0.90)
	Cisplatin-etoposide	95/173	112/178	0.86 (0.65–1.13)
Prior radiation schedule	Once daily	108/195	122/187	0.77 (0.60–1.00)
	Twice daily	31/69	47/79	0.72 (0.45–1.13)
Best response to prior cCRT	Complete response	15/31	18/34	1.00 (0.50–1.99)
	Partial response	106/191	130/200	0.81 (0.62–1.04)
	Stable disease	18/42	21/32	0.50 (0.26–0.94)
Prior PCI	Yes	65/142	84/143	0.73 (0.53–1.01)
	No	74/122	85/123	0.80 (0.59–1.09)



*End of chemotherapy or radiotherapy, whichever was latest.
Intention-to-treat analysis stratified, subgroup analyses unstratified. Not all prespecified subgroups are included in the plot.
Size of circle is proportional to number of events across both arms.

Exposure and safety summary

		Durvalumab (n=262)	Placebo (n=265)
Number of durvalumab or placebo doses	Median (range)	9.0 (1–26)	9.0 (1–26)
	Mean (standard deviation)	12.9 (9.6)	11.8 (9.2)
Any-grade all-cause AEs, n (%)		247 (94.3)	234 (88.3)
Maximum grade 3/4 AEs		64 (24.4)	64 (24.2)
Serious AEs		78 (29.8)	64 (24.2)
AEs leading to treatment discontinuation		43 (16.4)	28 (10.6)
AEs leading to death		7 (2.7)	5 (1.9)
Treatment-related* AEs leading to death		2 (0.8)‡	0
Any-grade immune-mediated AEs†		84 (32.1)	27 (10.2)
Maximum grade 3/4 immune-mediated AEs		14 (5.3)	4 (1.5)

Includes AEs with an onset date following first dose of study treatment, or pre-treatment AEs that increased in severity following first dose of study treatment, through to 90 days after last dose or until start of the first subsequent systemic anticancer therapy (whichever occurred first).
*Assessed by investigator. †Defined as an AE of special interest (excluding infusion related/hypersensitivity/anaphylactic reaction) that is consistent with an immune-mediated mechanism that required treatment with systemic corticosteroids, other immunosuppressants, or endocrine therapy. ‡Causes of death were encephalopathy and pneumonitis.

Conclusions

- **Durvalumab as consolidation treatment after cCRT demonstrated statistically significant and clinically meaningful improvement in OS and PFS compared with placebo in patients with LS-SCLC**
  - **OS HR 0.73** (95% CI 0.57–0.93), p=0.0104; mOS 55.9 (95% CI 37.3–NE) vs 33.4 (95% CI 25.5–39.9) months
  - **PFS HR 0.76** (95% CI 0.61–0.95), p=0.0161; mPFS 16.6 (95% CI 10.2–28.2) vs 9.2 (95% CI 7.4–12.9) months
  - Treatment benefit was generally consistent across predefined patient subgroups for both OS and PFS
- **Durvalumab consolidation treatment for up to 2 years was well tolerated, and safety findings were consistent with the known safety profile of durvalumab monotherapy in the post-cCRT setting**

Consolidation durvalumab will become the new standard of care for patients with LS-SCLC who have not progressed after cCRT

BARCELONA 2024 ESMO congress

Durvalumab as consolidation therapy in limited-stage SCLC (LS-SCLC): Outcomes by prior concurrent chemoradiotherapy (cCRT) regimen and prophylactic cranial irradiation (PCI) use in the ADRIATIC trial

Suresh Senan,[1] David Spigel,[2] Byoung Chul Cho,[3] Konstantin K. Laktionov,[4] Yoshitaka Zenke,[5] Ki Hyeong Lee,[6] Qiming Wang,[7] Alejandro Navarro,[8] Eva Lotte Buchmeier,[9] Sema Sezgin Goksu,[10] Andrzej Badzio,[11] Anhui Shi,[12] Davey B. Daniel,[13] Milada Zemanova,[14] Puneeth Iyengar,[15] Luis Paz-Ares,[16] Leah Szadkowski,[17] Priti Chugh,[18] W. Victoria Lai,[19] Ying Cheng[20]

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Phase 3 ADRIATIC trial subgroup analyses

Post-hoc analyses of durvalumab versus placebo in prespecified subgroups defined by PCI use and prior cCRT-related variables

PCI/cCRT components (in line with standards of care)*

- PCI delivered before randomisation, as clinically indicated
- Four cycles of platinum (cisplatin or carboplatin) and etoposide (three permitted†)
- RT: 60–66 Gy QD over 6 weeks or 45 Gy BID over 3 weeks‡

ITT population	Durvalumab (n = 264)	Placebo (n = 266)
Received PCI, %	54	54
Carboplatin / cisplatin CT,§ %	34 / 66	33 / 67
BID / QD thoracic RT, %	26 / 74	30 / 70

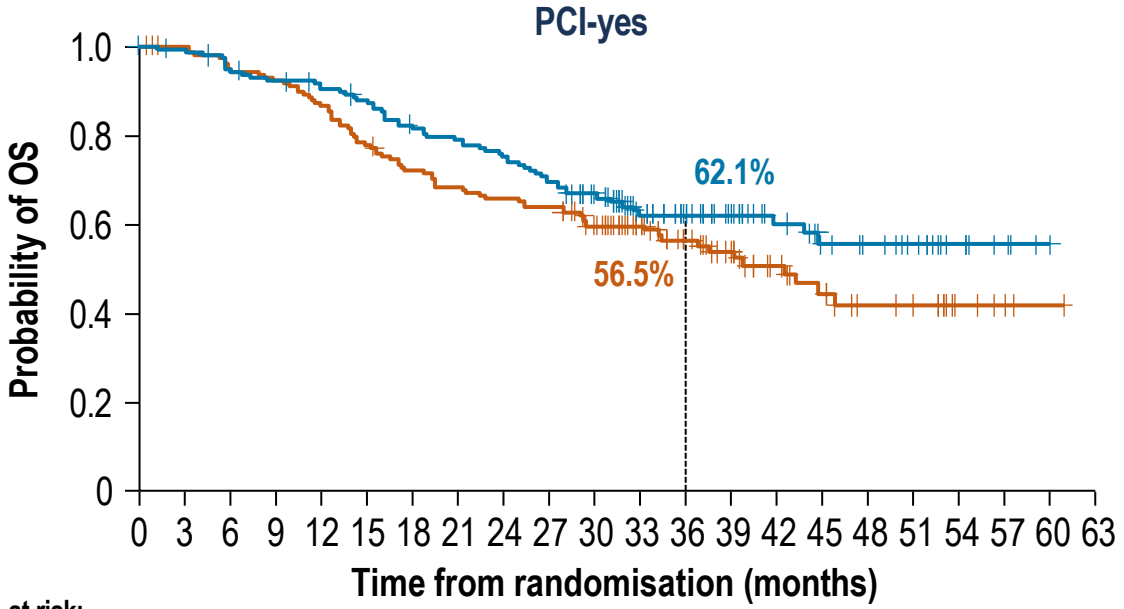
- Analyses of OS, PFS, and safety with durvalumab vs placebo in subgroups of patients who received:
  - PCI or no PCI
  - Carboplatin- or cisplatin-based CT
  - BID or QD RT
- Multivariable analyses: for each subgroup, HRs for durvalumab vs placebo were calculated from an unstratified multivariable Cox proportional hazards model with a treatment-by-subgroup (PCI, CT, or RT) interaction term that was adjusted for PCI, CT, RT, time from cCRT to randomisation, response to cCRT, age, sex, WHO PS, and disease stage

BID, twice daily; CT, chemotherapy; Gy, gray; HR, hazard ratio; ITT, intention-to-treat; QD, once daily; RT, radiotherapy.

*The components and delivery of standard of care may vary based on patient characteristics and region.
†If disease control was achieved and no additional benefit was expected with an additional cycle of CT, in the opinion of the investigator.
‡RT must commence no later than end of cycle 2 of CT. §Based on the first cycle of CT.

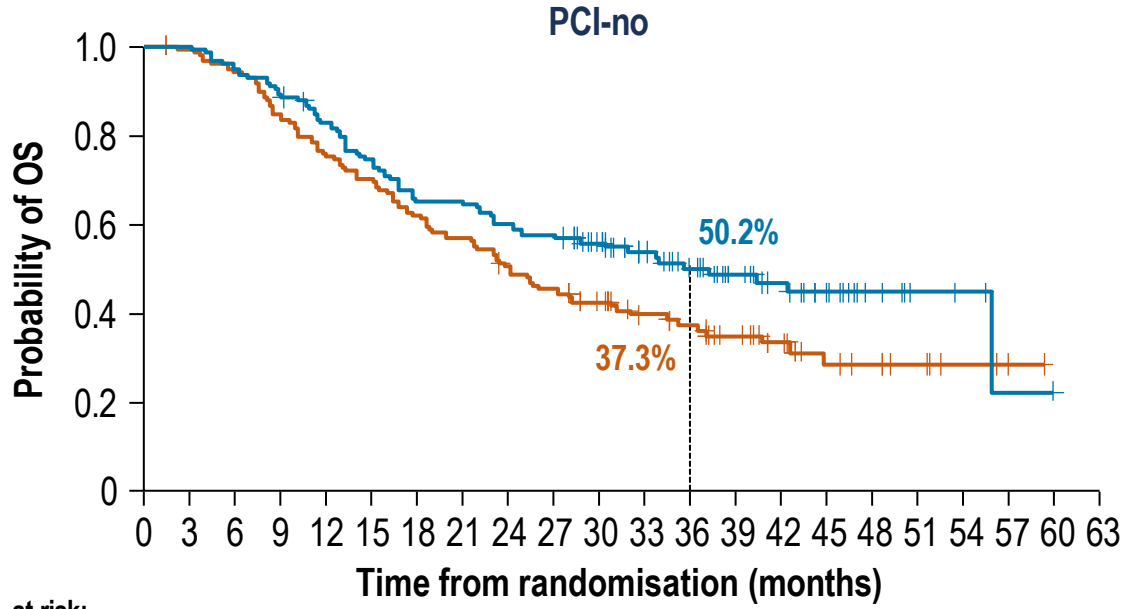
PCI-yes and PCI-no subgroups – OS

	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 (0.52–1.07)*		0.71 (0.51–0.99)*		0.73 (0.57–0.93)†	
Multivariable HR (95% CI)	0.72 (0.50–1.03)‡		0.73 (0.52–1.02)‡		–	



No. at risk:

D, PCI-yes	142	139	132	127	124	118	110	105	100	93	82	63	51	40	29	23	19	15	8	4	1	0
P, PCI-yes	143	140	133	129	122	110	100	95	91	89	77	61	48	37	26	20	14	13	5	3	1	0



No. at risk:

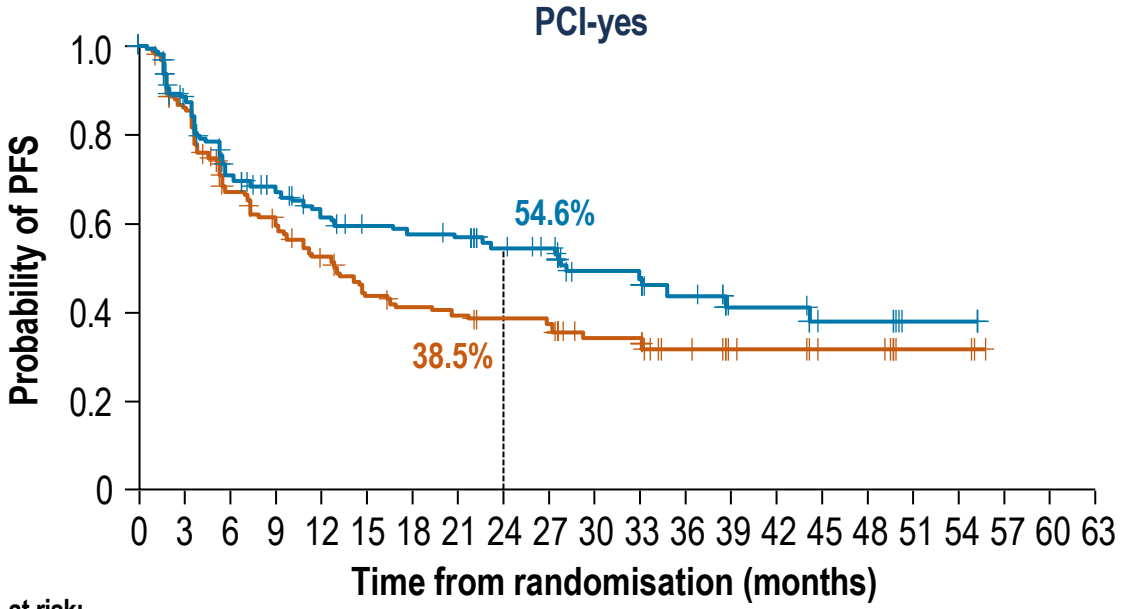
D, PCI-no	122	122	116	109	99	89	79	78	72	69	59	47	39	28	22	16	8	4	3	1	0	0
P, PCI-no	123	120	114	102	92	85	75	69	60	54	46	36	32	25	18	11	9	6	3	2	0	0

*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.

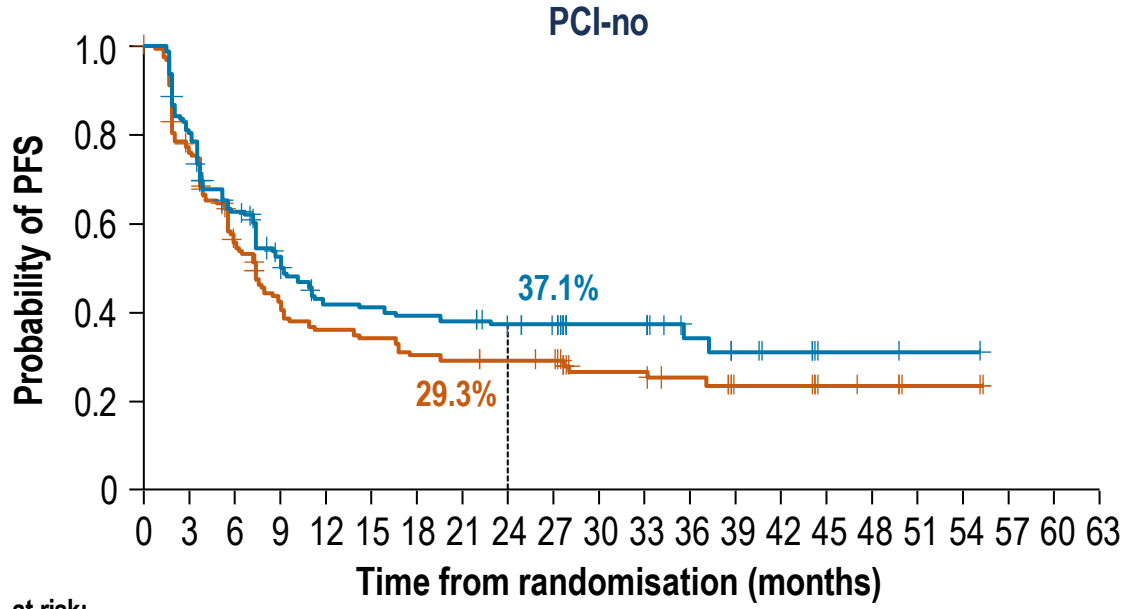
PCI-yes and PCI-no subgroups – PFS

	PCI-yes		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 (0.52–1.00)*		0.80 (0.59–1.09)*		0.76 (0.61–0.95)†	
Multivariable HR (95% CI)	0.72 (0.52–0.99)‡		0.84 (0.61–1.15)‡		–	



No. at risk:

D, PCI-yes	142	114	89	79	70	63	61	59	50	47	31	31	21	13	13	8	8	3	3	0	0	0
P, PCI-yes	143	116	84	76	62	52	47	45	42	41	28	28	18	13	12	9	9	3	3	0	0	0



No. at risk:

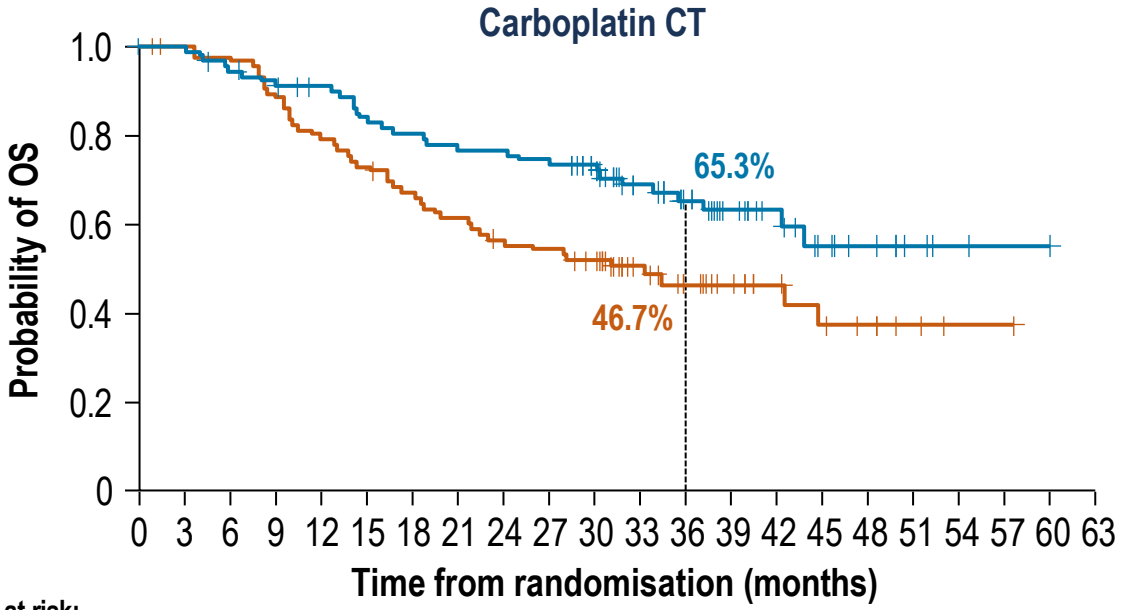
D, PCI-no	122	98	72	56	43	42	40	39	34	31	20	20	12	8	6	2	2	1	1	0	0	0
P, PCI-no	123	92	62	46	38	36	32	31	29	28	19	19	16	10	10	6	5	2	2	0	0	0

*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.

TNM, Tumour-Node-Metastasis.

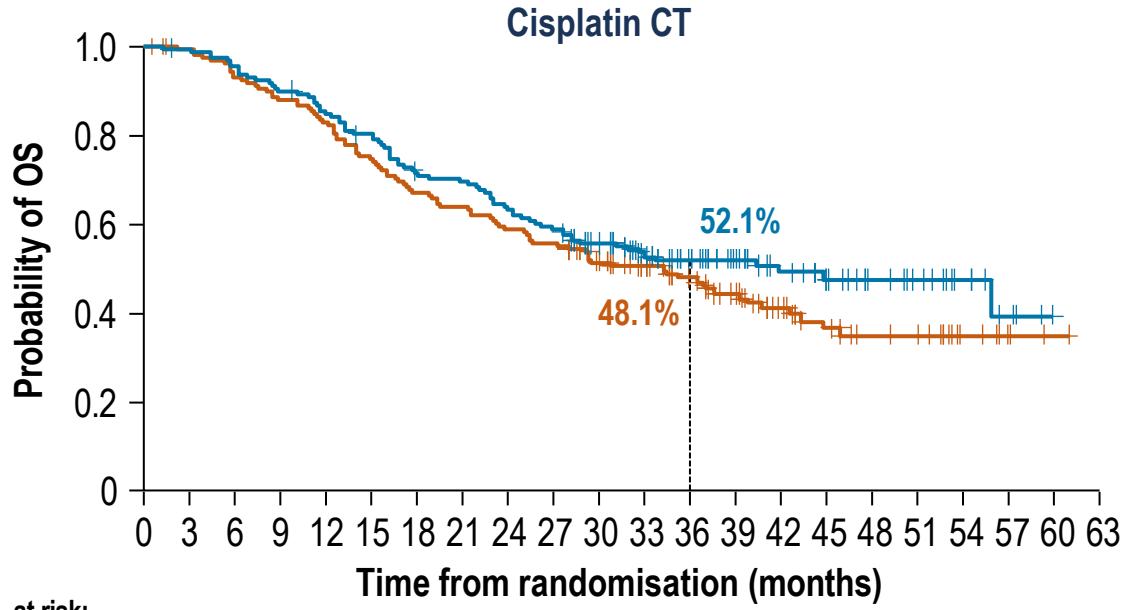
Carboplatin and cisplatin CT subgroups – OS

	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 (0.35–0.89)*		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)‡		–	



No. at risk:

D, carboplatin	91	90	84	81	77	71	68	66	65	63	55	40	32	23	17	11	8	4	2	1	1	0
P, carboplatin	88	86	84	77	69	63	57	52	47	45	41	28	22	16	11	8	6	3	1	1	0	0



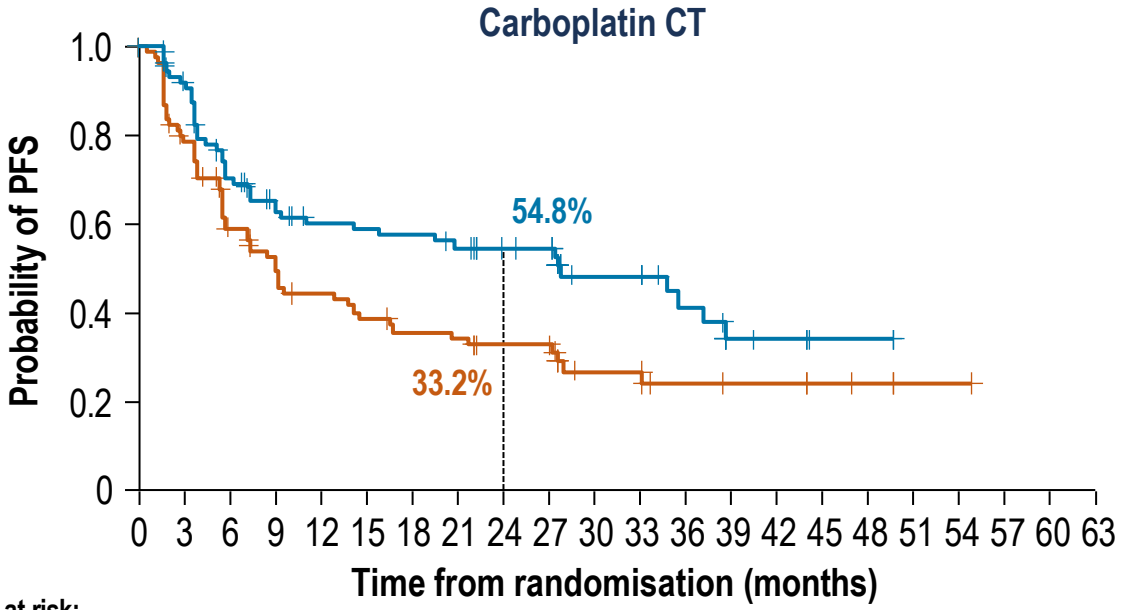
No. at risk:

D, cisplatin	173	171	164	155	146	136	121	117	107	99	86	70	58	45	34	28	19	15	9	4	0	0
P, cisplatin	178	174	163	154	145	132	118	112	104	98	82	69	58	46	33	23	17	16	7	4	1	0

*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.

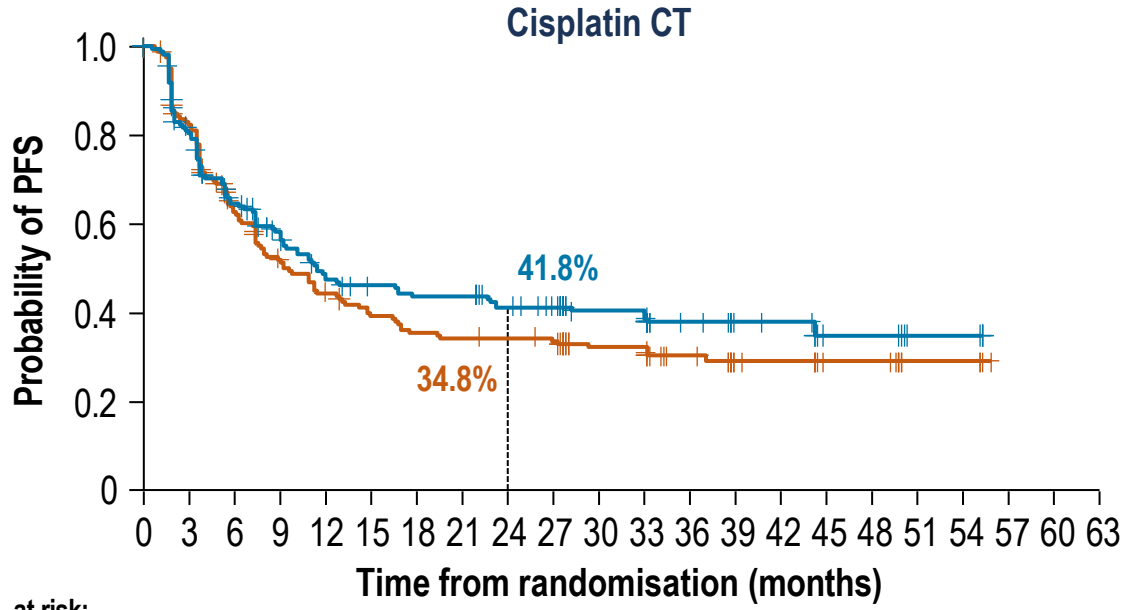
Carboplatin and cisplatin CT subgroups – PFS

	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 (0.41–0.90)*		0.86 (0.65–1.13)*		0.76 (0.61–0.95)†	
Multivariable HR (95% CI)	0.60 (0.40–0.88)‡		0.89 (0.67–1.17)‡		–	



No. at risk:

D, carboplatin	91	79	59	50	43	42	41	38	33	32	18	18	12	6	5	2	2	0	0	0	0	0
P, carboplatin	88	67	46	39	32	28	25	24	20	20	11	11	7	6	6	4	3	1	1	0	0	0



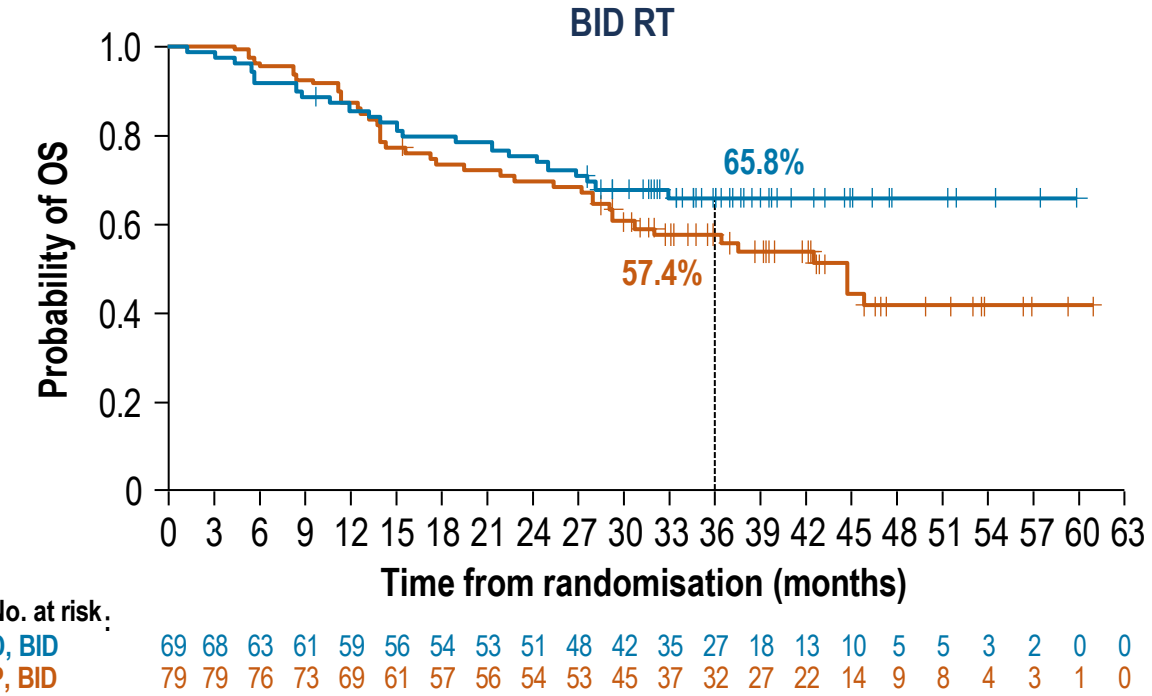
No. at risk:

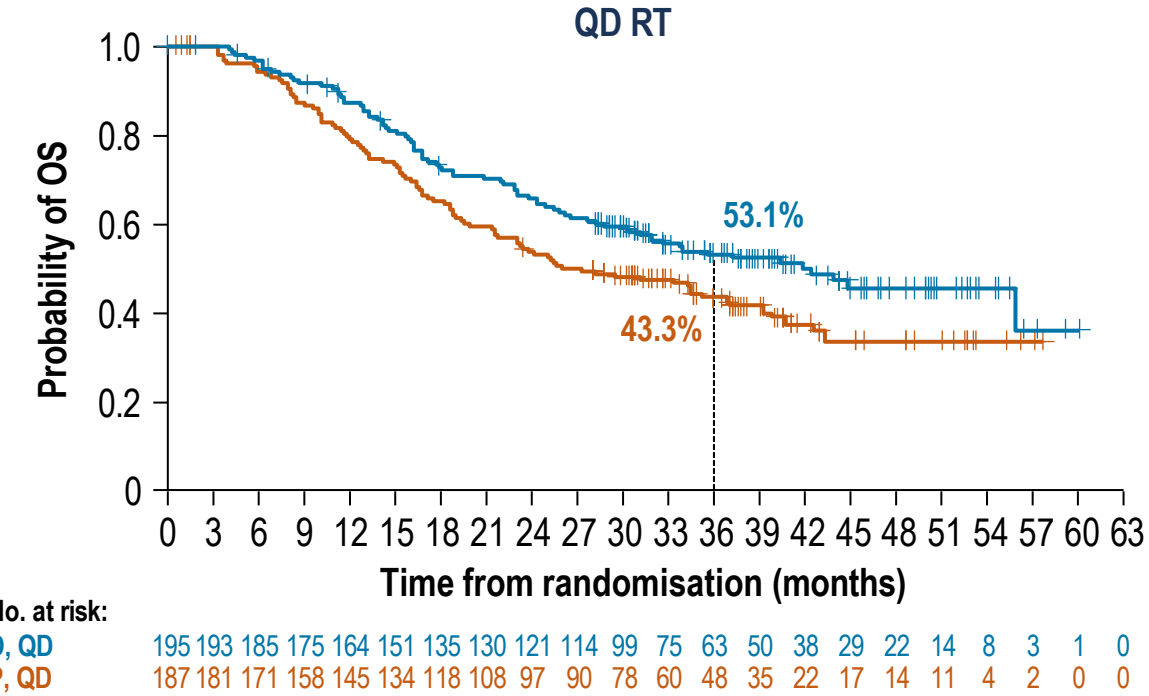
D, cisplatin	173	133	102	85	70	63	60	60	51	46	33	33	21	15	14	8	8	4	4	0	0	0
P, cisplatin	178	141	100	83	68	60	54	52	51	49	36	36	27	17	16	11	11	4	4	0	0	0

*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.

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 (0.40–1.14)*		0.72 (0.55–0.96)*		0.73 (0.57–0.93)†	
Multivariable HR (95% CI)	0.71 (0.42–1.18)‡		0.73 (0.55–0.96)‡		–	

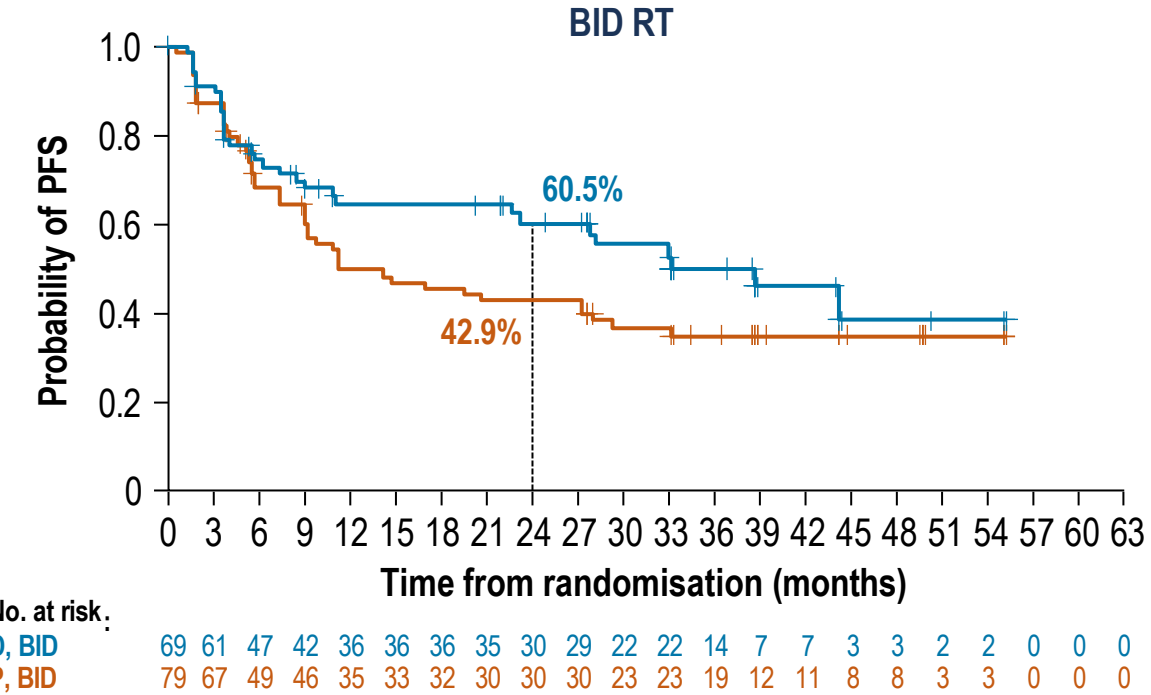




*Subgroup HRs and CIs calculated using an unstratified Cox proportional hazards model.
†ITT HR and CIs calculated using a Cox proportional hazards model stratified by receipt of PCI.
‡Multivariable analysis interaction p-value 0.95.

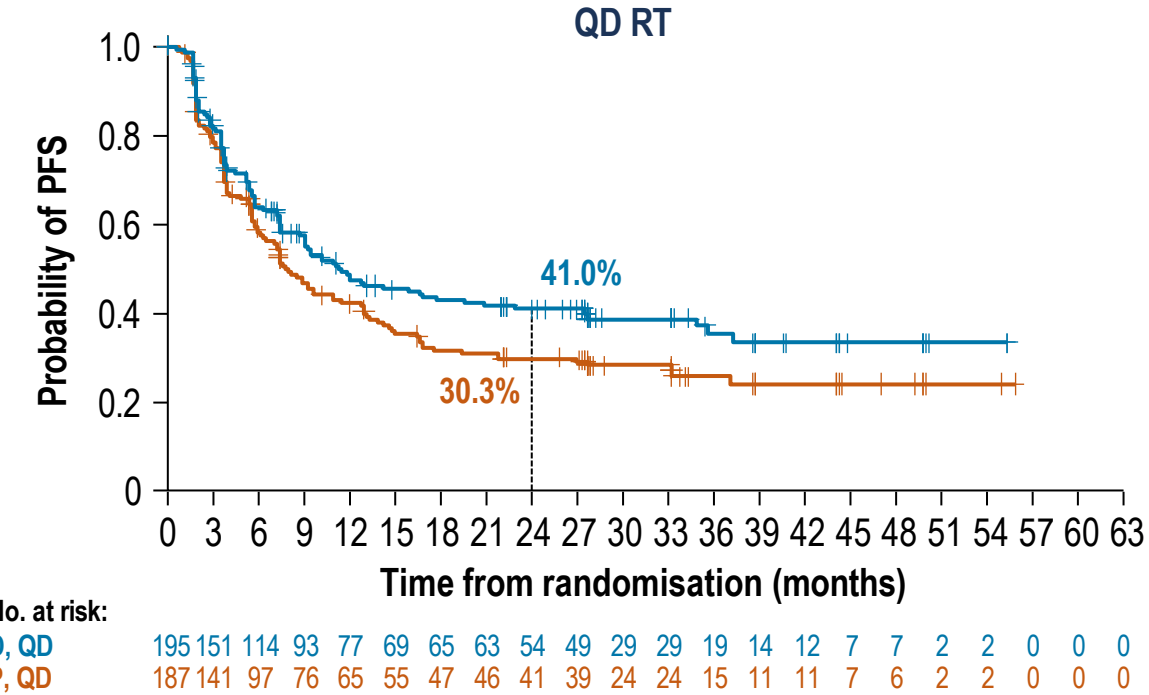
BID and QD RT subgroups – PFS

	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 (0.45–1.13)*		0.77 (0.60–1.00)*		0.76 (0.61–0.95)†	
Multivariable HR (95% CI)	0.73 (0.46–1.14)‡		0.79 (0.61–1.03)‡		–	



No. at risk:

D, BID	69	61	47	42	36	36	36	35	30	29	22	22	14	7	7	3	3	2	2	0	0	0
P, BID	79	67	49	46	35	33	32	30	30	30	23	23	19	12	11	8	8	3	3	0	0	0

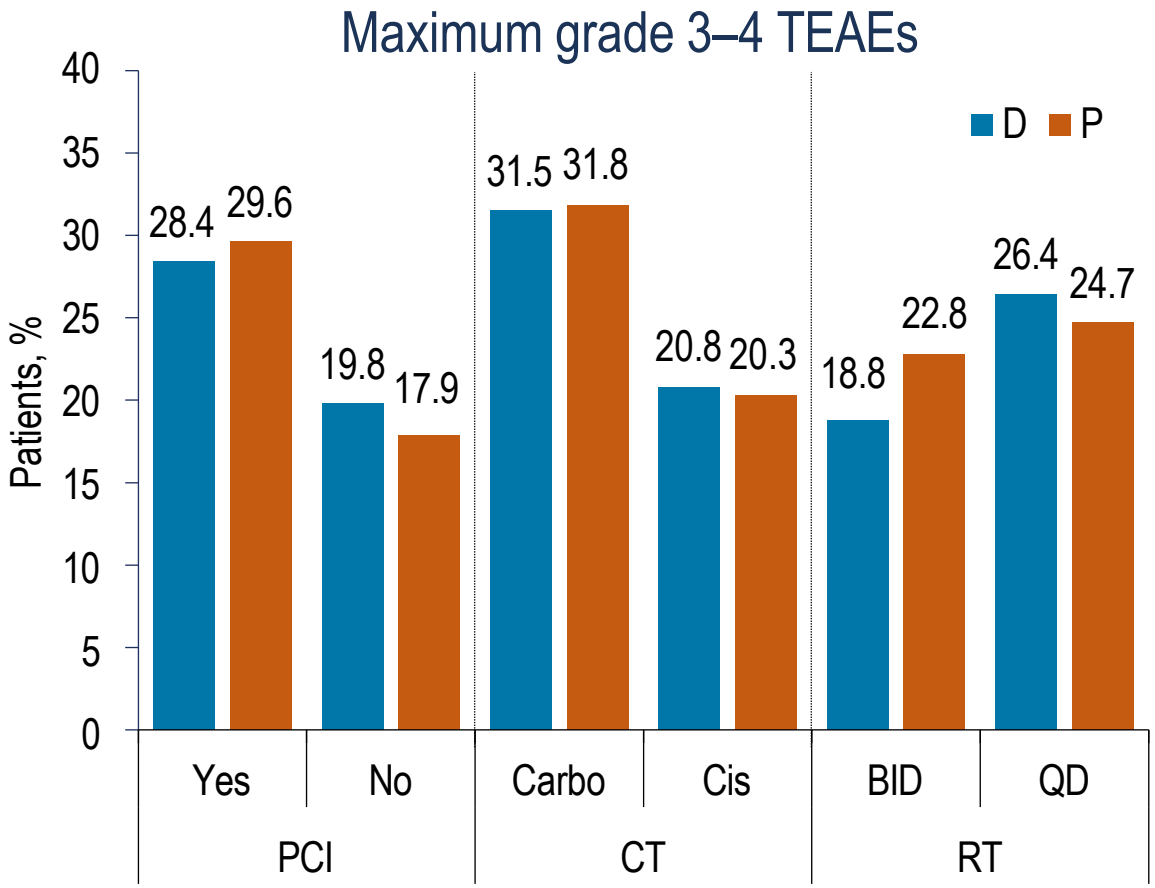


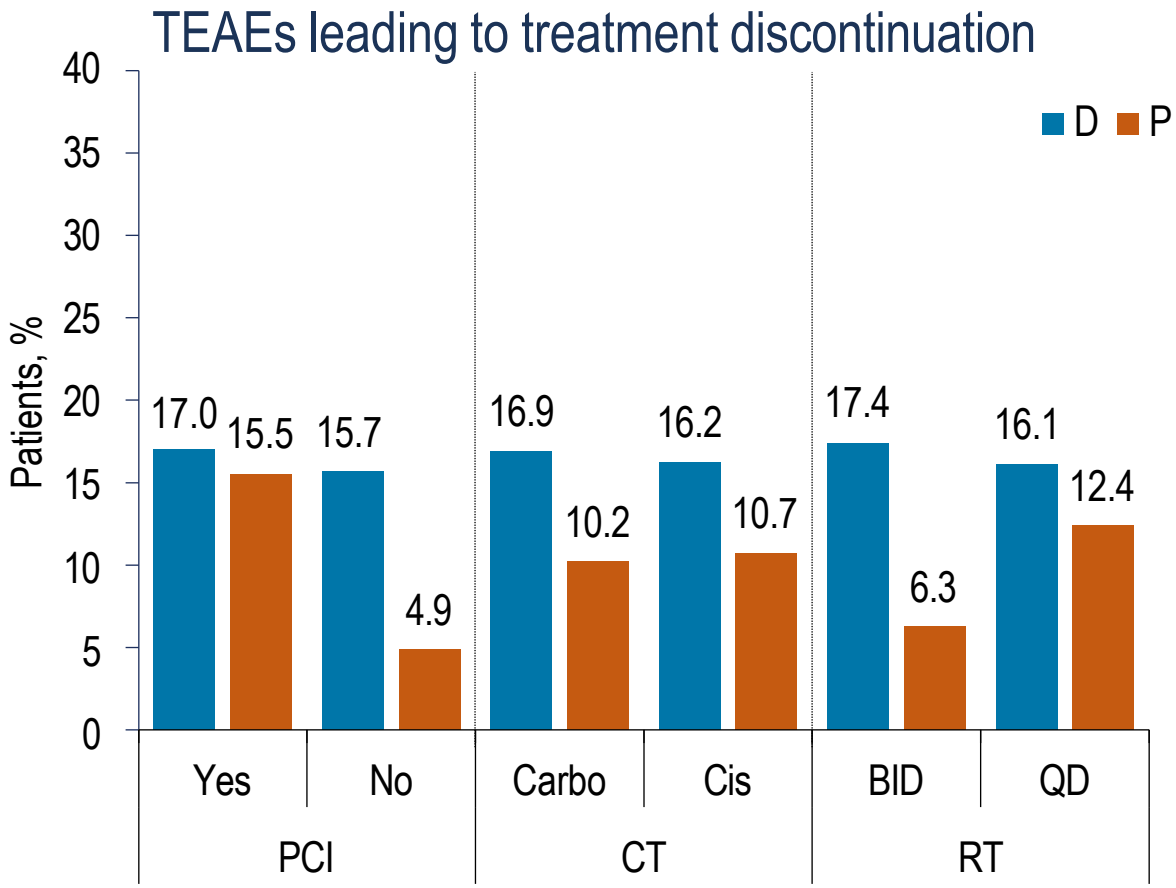
No. at risk:

D, QD	195	151	114	93	77	69	65	63	54	49	29	29	19	14	12	7	7	2	2	0	0	0
P, QD	187	141	97	76	65	55	47	46	41	39	24	24	15	11	11	7	6	2	2	0	0	0

*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.

Safety profile by subgroup





- Rates of maximum grade 3–4 TEAEs higher in PCI-yes vs PCI-no and carboplatin vs cisplatin subgroups; rates of TEAEs leading to durvalumab discontinuation similar across subgroups
- No meaningful differences in safety profiles between BID and QD subgroups

TEAE, treatment-emergent adverse event.

Conclusions

- **Consolidation durvalumab consistently improved OS and PFS vs placebo across presented subgroups**
  - Magnitude of benefit with durvalumab vs placebo was consistent within PCI and RT subgroups and varied somewhat between CT subgroups
    - Multivariable analyses showed no significant interactions between durvalumab treatment effect and PCI or cCRT subgroups
- **Safety profiles were generally consistent across all subgroups**

Durvalumab demonstrated consistent benefit vs placebo irrespective of prior PCI use and cCRT components, further supporting consolidation durvalumab as the new standard of care in LS-SCLC

Update treatment of LD of SCLC

Limited disease

Concurrent CTx(Etoposide + platinum) + RTx followed by PCI

Consolidation Tx ; Durvalumab

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2025
Small Cell Lung Cancer

NCCN Guidelines Index
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Discussion

PRINCIPLES OF SYSTEMIC THERAPY

PRIMARY OR ADJUVANT THERAPY FOR LIMITED STAGE SCLC:

Four cycles of cytotoxic chemotherapy are recommended.
Planned cycle length should be every 21–28 days during concurrent RT.
During cytotoxic chemotherapy + RT, cisplatin/etoposide is recommended (category 1).
The use of myeloid growth factors is not recommended during concurrent cytotoxic chemotherapy therapy plus RT (category 1 for not using GM-CSF).[1]

Preferred Regimens

- **Cisplatin 75 mg/m² day 1 and etoposide 100 mg/m² days 1, 2, 3[2]**
- **Cisplatin 60 mg/m² day 1 and etoposide 120 mg/m² days 1, 2, 3[3]**
- **Consolidation Therapy**
  - **Durvalumab 1500 mg day 1 every 28 days (category 1)[a,4]**

Other Recommended Regimens

- **Cisplatin 25 mg/m² days 1, 2, 3 and etoposide 100 mg/m² days 1, 2, 3[2]**
- **Carboplatin area under the curve (AUC) 5–6 day 1 and etoposide 100 mg/m² days 1, 2, 3[b,5]**

2025년 4월 4일 부터,

제한병기 소세포폐암† 환자에게도 임핀지® 치료가 가능해졌습니다.[1]

안녕하세요 선생님,

항상 진료와 연구에 매진하시는 선생님들께 감사 드립니다.

2025년 4월 4일, 임핀지®가 백금 기반 화학방사선 요법(CRT) 이후 질병이 진행되지 않은 제한병기 소세포폐암 환자를 위한 치료요법으로 승인되었습니다.[1]

지난 30년간 전신 치료제가 부족했던 제한병기 소세포폐암 치료에, 임핀지®는 위약대비 22.5 개월의 추가적인 mOS를 제공하게 되었습니다.[2]

이제 비소세포폐암 뿐 아니라 제한병기 소세포 폐암 환자까지 임핀지®의 치료 혜택을 누릴 수 있도록 최선을 다하겠습니다.

감사합니다.

IMFINZI®
durvalumab
Injection for Intravenous Use 50 mg/mL

†각 적응증 별 상세 내용은 제품 설명서를 참고해 주시기 바랍니다.

약제비 환급 프로그램

KBDCA 사단법인 한국혈액암협회

임핀지 주(120mg, 500mg) 이뮤도 주(300mg) 약제비 환급 프로그램 안내

1. 지원 대상 : A. 임핀지주, 이뮤도주를 허가사항내 전액본인부담(100/100)으로 투여 받은 환자
   B. 기타(건강보험심사평가원의 '허가초과 항암요법'에 해당하는 경우)에 해당하는 환자이면서, 임핀지 주, 이뮤도 주를 전액본인부담(100/100)으로 투여받은 환자
2. 지원내용 : 임핀지주, 이뮤도주를 전액본인부담 (상한가 기준)으로 처방받아 구매한 내용에 대해서 일부 금액을 환자에게 환급
3. 지원기간 : 2020년 4월 1일 ~ 해당 환급 프로그램 종료시 까지
4. 지원기준 : *임핀지 주
   (허가사항 내) 담도암, 간세포암, 제한기 소세포폐암, 절제가능한 비소세포폐암, 자궁내막암
   월 건강보험료 납부액이 90만원 이하인 환자 : 위험분담제 계약 및 환자 약제비 지원프로그램에 의한 환급액
   월 건강보험료 납부액이 90만원 초과인 환자 : 위험분담제 계약상의 환급액
   (허가사항 내) 절제불가능한 비소세포폐암, 확장기 소세포폐암 : 위험분담제 계약상의 환급액
   *이뮤도 주 : (허가사항내) 간세포암 : 환자 약제비 지원프로그램에 의한 환급액
   * 단, 본 지원내용은 예고없이 변경 또는 종료될 수 있습니다.
5. 진행과정 : 신청서류 준비 ▶ 우편접수 ▶ 서류심사 ▶ 환급
6. 신청서류 다운로드 경로 : 한국혈액암협회 홈페이지(www.kbdca.or.kr) 접속 후 약제비 지원 아이콘 클릭 ▶ 약제비지원(종양) ▶ 더발루맙(RSA),트레멜리무맙 "자세히보기" ▶ 하단 신청서식 관련 서류 모두 다운로드 후 출력
7. 약제비 신청서류
   ① 임핀지/이뮤도 주 약제비 환급 신청서 (최초 신청 시)
   ② 의료진 추천서 (최초 신청 시)
   ③ 개인정보 처리 동의서 (최초 신청 시)
   ④ 비밀유지확약서 : 총3부 작성 후, 2부 (협회, 회사보관용) 협회 접수
   ⑤ 진단서 원본 (최초 신청 시)
   ⑥ 건강보험 관련 서류 (택 1)
   (1) (환자가 부양자일 경우) 건강보험료 납부확인서 (2) (환자가 피부양자일 경우) 건강보험료 납부확인서와 건강보험자격확인서
   ⑦ 환자 본인 명의 통장사본 (최초 신청 시)
   ⑧ 임핀지주 약제명이 나와있는 진료비 세부내역서 (최초 신청 시 / 매 신청 시)
   ※ 간세포암이신 경우 임핀지 주 및 이뮤도 주 약제명이 나와있는 진료비 세부내역서 (최초 신청시 / 매 신청시)
   ⑨ 병원 수납 영수증 원본 (최초 신청 시 / 매 신청 시)
   ※ 매 신청 시, 본인 부담으로 구입하여 투약한 것을 증빙할 수 있는 진료비 세부내역서와 병원 수납영수증 원본을 함께 제출하셔야 합니다.

※ 꼭 알아두어야 할 사항
1. 첨부서류는 하나도 빠짐없이 준비되어야만 지원 가능합니다.
2. 지급은 적정성 심사 후 특별한 사유가 없는 한 접수일을 기준으로 30일 내외에 완료됩니다.
3. 환자 본인 통장으로 환급이 불가한 경우에는 협회로 문의 바랍니다. (환자 사망 시에도 포함)
4. 환급금을 타인에게 알릴 경우, 비밀 유지 의무 위반에 해당되므로 주의 바랍니다.
5. 허위 보고나 그밖의 부당한 방법으로 환급 신청 시 불이익을 받으실 수 있습니다.
6. 모든 서류는 우편으로 접수 바랍니다.

본 환자 지원 프로그램에 대한 자세한 문의는 한국혈액암협회 임핀지 주, 이뮤도 주 환급 프로그램 담당자에게 문의해 주시길 바랍니다.

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JEONBUK NATIONAL UNIVERSITY HOSPITAL

의료에 신뢰를 더하다. JBUH+

Contents

Treatment of SCLC

Limited disease

Concurrent CTx(Etoposide + platinum) + RTx followed by PCI

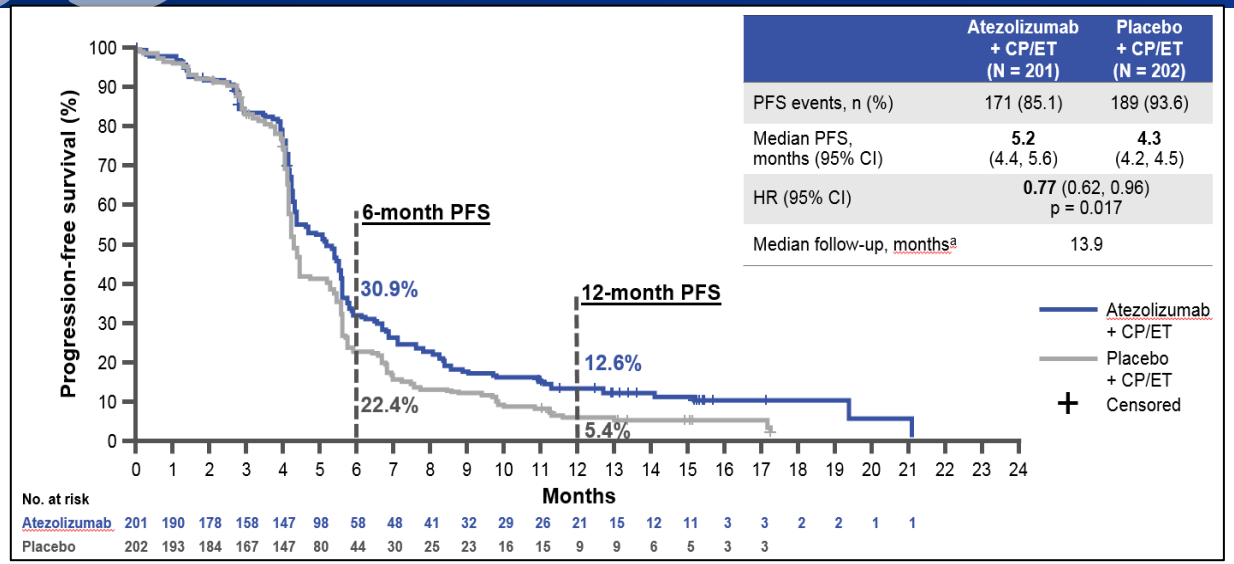
Consolidation Tx ; Durvalumab

Extensive disease

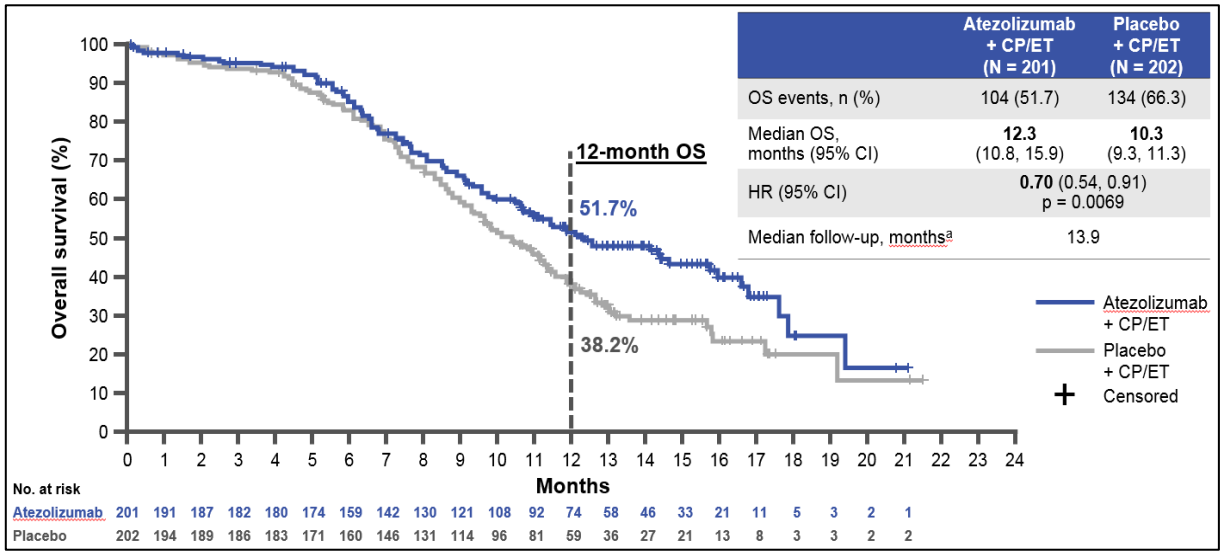
Ist line Tx : ImmunoTx + Etoposide/platinum CTx → ImunoTx maintenance
IMPOWER 133, CASPIAN study

$2^{nd}/3^{rd}$ line Tx

IMpower-133



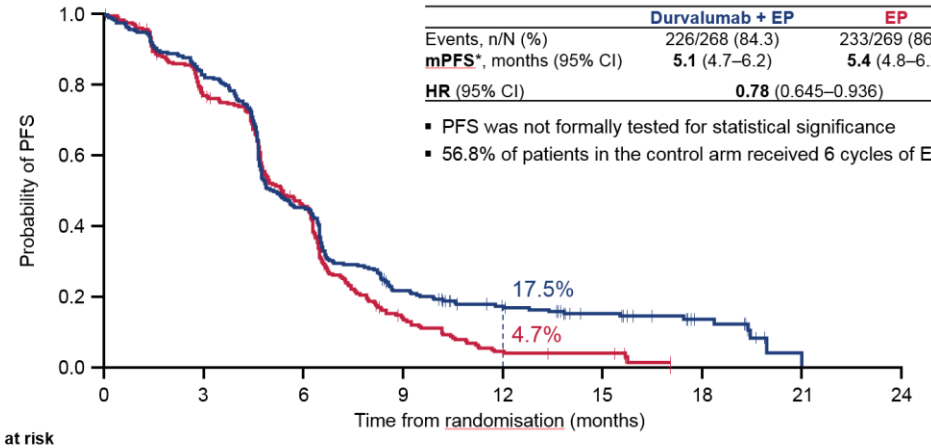
	Atezolizumab + CP/ET (N = 201)	Placebo + CP/ET (N = 202)
PFS events, n (%)	171 (85.1)	189 (93.6)
Median PFS, months (95% CI)	**5.2** (4.4, 5.6)	**4.3** (4.2, 4.5)
HR (95% CI)	**0.77** (0.62, 0.96) p = 0.017	
Median follow-up, months[a]	13.9	



	Atezolizumab + CP/ET (N = 201)	Placebo + CP/ET (N = 202)
OS events, n (%)	104 (51.7)	134 (66.3)
Median OS, months (95% CI)	**12.3** (10.8, 15.9)	**10.3** (9.3, 11.3)
HR (95% CI)	**0.70** (0.54, 0.91) p = 0.0069	
Median follow-up, months[a]	13.9	

CASPIAN

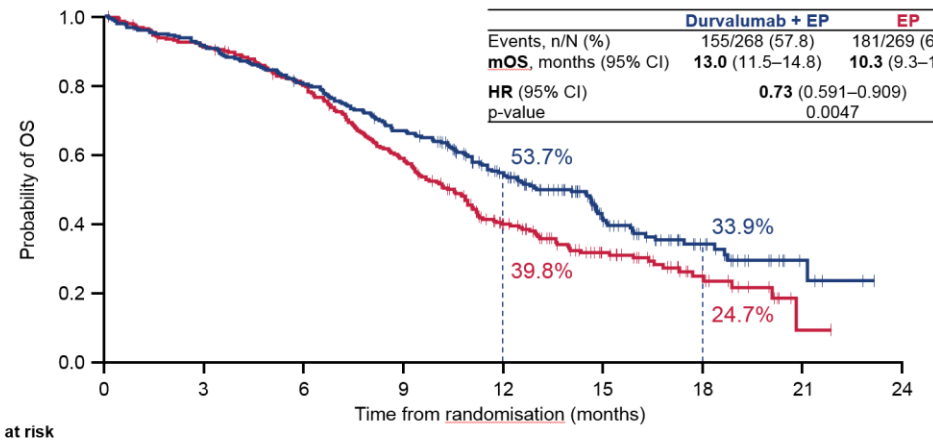
Progression-free Survival



	Durvalumab + EP	EP
Events, n/N (%)	226/268 (84.3)	233/269 (86.6)
mPFS*, months (95% CI)	**5.1** (4.7–6.2)	**5.4** (4.8–6.2)
HR (95% CI)	**0.78** (0.645–0.936)	

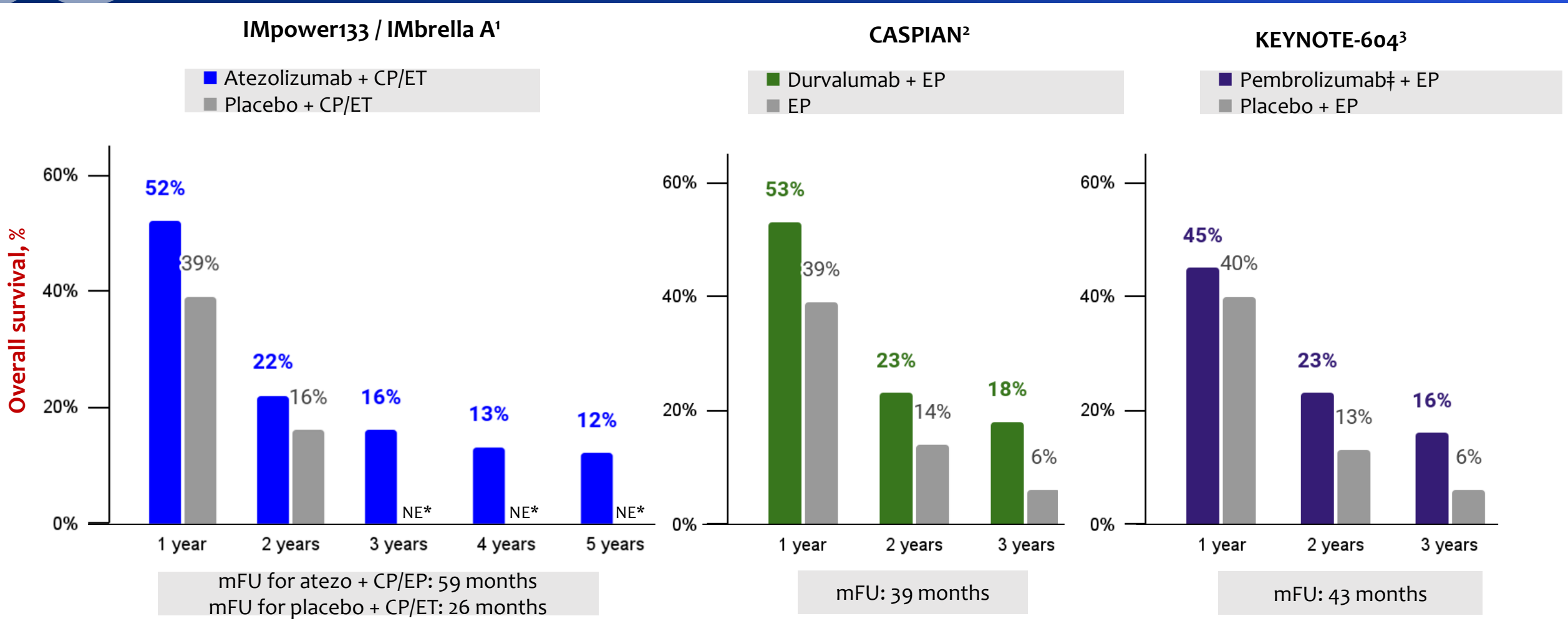
- PFS was not formally tested for statistical significance
- 56.8% of patients in the control arm received 6 cycles of EP

Overall Survival (Primary Endpoint)



	Durvalumab + EP	EP
Events, n/N (%)	155/268 (57.8)	181/269 (67.3)
mOS, months (95% CI)	**13.0** (11.5–14.8)	**10.3** (9.3–11.2)
HR (95% CI)	**0.73** (0.591–0.909)	
p-value	0.0047	

Overall survival rates across SCLC trials



These are not head-to-head trials; due to different trial designs and study populations, direct comparisons should be avoided.

*≥3 year OS rates were NE in the placebo + CP/ET arm (no roll-over to IMbrella A); ‡Treatment up to 35 cycles (~2 years)
CP, carboplatin; EP, etoposide + platinum; ET, etoposide; mFU, median follow-up; NE, not estimable; OS, overall survival

•1. Liu, et al. WCLC 2023 (Abs OA01.04); 2. Paz-Ares, et al. ESMO Open 2022, 3. Rudin, et al. WCLC 2022 (Abs OA12.06)

Cross-Trial Comparison: Immune-Related AEs

Immune-Related AE, n (%)	IMpower133[1]		CASPIAN[2]	
	Atezo + EP (n = 198)	Placebo + EP (n = 196)	Durva + EP (n = 265)*	EP (n = 266)
Any	82 (41.4)	48 (24.5)	53 (20)	7 (3)
Hypothyroid events	25 (12.6)	1 (0.5)	24 (9)	2 (1)
Hyperthyroid events	11 (5.6)	5 (2.6)	14 (5)	0
Diarrhea/colitis	3 (1.5)	0	5 (2)	1 (<1)
Dermatitis/rash	40 (20.2)	21 (10.7)	5 (2)	2 (1)
Hepatic events	15 (7.6)	9 (4.6)	7 (3)	0
Pneumonitis	5 (2.5)	5 (2.6)	7 (3)	2 (1)
Adrenal insufficiency	0	3 (1.5)	2 (1)	0
Thyroiditis	NR	NR	4 (2)	0
Type 1 diabetes	NR	NR	4 (2)	0
Hypophysitis	NR	NR	0	0
Pancreatic events	NR	NR	1 (<1)	0
Myocarditis	NR	NR	0	0
Other rare/miscellaneous	NR	NR	0	0
IRR	11 (5.6)	10 (5.1)	NR	NR

*Grade 5 irAEs in 2 patients receiving durva + EP (1 each of hepatotoxicity and interstitial lung disease) and 1 patient receiving EP (pneumonitis)

1. Liu. JCO. 2021;39:619. 2. Goldman. Lancet Oncol. 2021;22:51.

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Cancer Res Treat. 2024;56(2):422-429

Original Article

The Real-World Outcome of First Line Atezolizumab in Extensive-Stage Small Cell Lung Cancer: A Multicenter Prospective Cohort Study

Myeong Geun Choi[1,2], **Yeon Joo Kim**[3], **Jae Cheol Lee**[4], **Wonjun Ji**[1], **In-Jae Oh**[5], **Sung Yong Lee**[6], **Seong Hoon Yoon**[7], **Shin Yup Lee**[8], **Jeong Eun Lee**[9], **Eun Young Kim**[10], **Chang-Min Choi**[1,4]

Table 2. Effectiveness assessment of the atezolizumab plus chemotherapy treatment

Variable	RW-ACE (n=100)	IMpower133 (n=201)
Median follow-up duration (mo)	13.2 (6.6-22.4)	13.9 (N/E-N/E)
Best response		
Complete response	0	5 (2.5)
Partial response	67 (67.0)	116 (57.7)
Stable disease	15 (15.0)	42 (20.9)
Progressive disease	11 (11.0)	22 (10.9)
Not evaluated	7 (7.0)	16 (8.0)
Objective response rate (%)	67.0	60.2
Disease control rate (%)	82.0	78.6
Median PFS (mo)	6.0 (4.2-11.0)	5.2 (4.4-5.6)
Median OS (mo)	13.5 (7.8-not reached)	12.3 (10.8-15.9)
OS rate at 1-year (%)	57.8	51.7

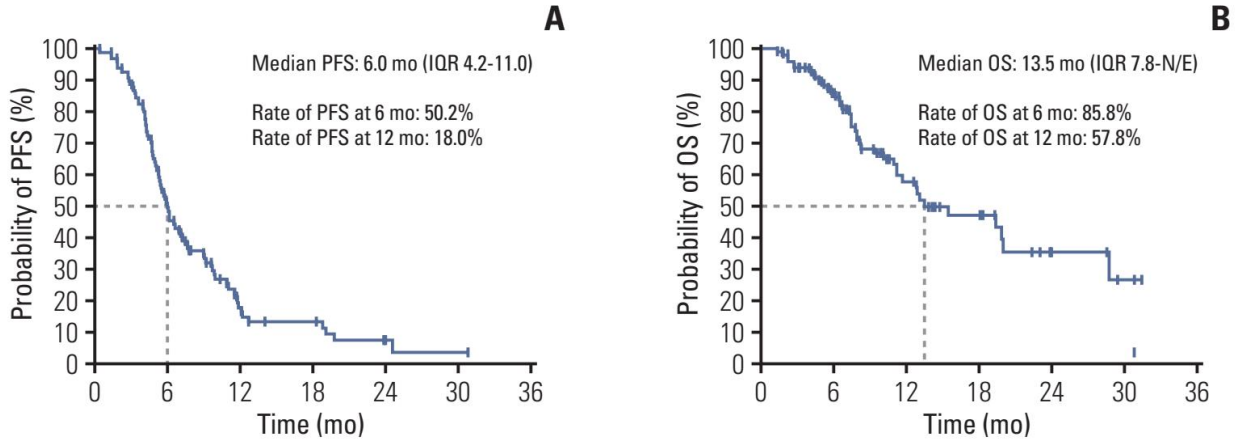


Fig. 2. Progression-free survival (PFS) (A) and overall survival (OS) (B) for all patients with small cell lung cancer receiving atezolizumab plus chemotherapy. IQR, interquartile range; N/E, not evaluable.

Update treatment of ED of SCLC

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2025
Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRIMARY THERAPY FOR EXTENSIVE STAGE SCLC[c]:

Four cycles of cytotoxic chemotherapy are recommended, but some patients may receive up to 6 cycles based on response and tolerability after 4 cycles.

Preferred Regimens

- Carboplatin AUC 5 day 1 and etoposide 100 mg/m² days 1, 2, 3 and atezolizumab 1200 mg day 1 every 21 days x 4 cycles followed by maintenance atezolizumab 1200 mg day 1, every 21 days (category 1 for all)[d,e,k,6]
- Carboplatin AUC 5 day 1 and etoposide 100 mg/m² days 1, 2, 3 and atezolizumab 1200 mg day 1 every 21 days x 4 cycles followed by maintenance atezolizumab 1680 mg day 1, every 28 days[d,e,k]
- Carboplatin AUC 5–6 day 1 and etoposide 80–100 mg/m² days 1, 2, 3 and durvalumab 1500 mg day 1 every 21 days x 4 cycles followed by maintenance durvalumab 1500 mg day 1 every 28 days (category 1 for all)[d,e,f,7]
- Cisplatin 75–80 mg/m² day 1 and etoposide 80–100 mg/m² days 1, 2, 3 and durvalumab 1500 mg day 1 every 21 days x 4 cycles followed by maintenance durvalumab 1500 mg day 1 every 28 days (category 1 for all)[d,e,f,7]

Other Recommended Regimens

- Carboplatin AUC 5–6 day 1 and etoposide 100 mg/m² days 1, 2, 3[8]
- Cisplatin 75 mg/m² day 1 and etoposide 100 mg/m² days 1, 2, 3[9]
- Cisplatin 80 mg/m² day 1 and etoposide 80 mg/m² days 1, 2, 3[10]
- Cisplatin 25 mg/m² days 1, 2, 3 and etoposide 100 mg/m² days 1, 2, 3[11]

Useful in Certain Circumstances

- Carboplatin AUC 5 day 1 and irinotecan 50 mg/m² days 1, 8, 15[12]
- Cisplatin 60 mg/m² day 1 and irinotecan 60 mg/m² days 1, 8, 15[13]
- Cisplatin 30 mg/m² days 1, 8 and irinotecan 65 mg/m² days 1, 8[14]

Footnotes (SCL-E 2 of 6)
Subsequent Systemic Therapy (SCL-E 3 of 6)
Response Assessment (SCL-E 4 of 6)
References (SCL-E 5 of 6)

TMB and PD-L1 appear not to be predictive of outcomes

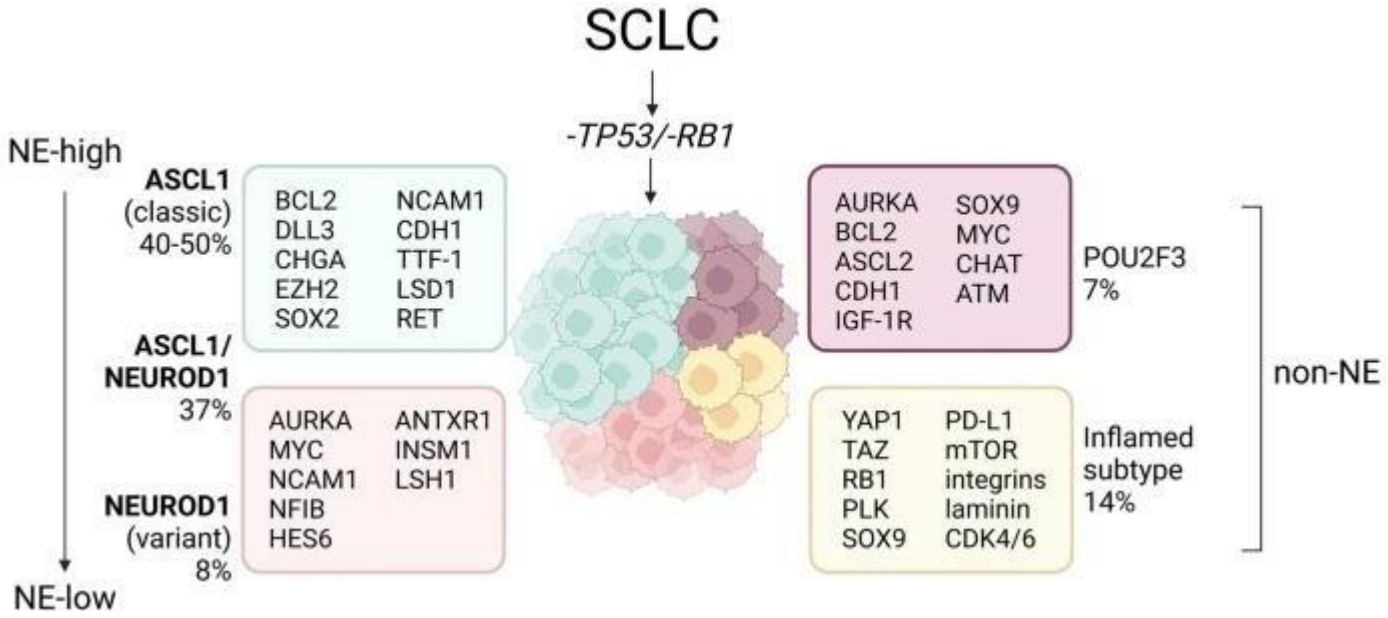
	IMpower133[1] Atezolizumab + CP/ET	CASPIAN[2,3] Durvalumab + EP ± tremelimumab		KEYNOTE-604[4] Pembrolizumab* + EP
Median follow-up	22.9 months	14.2 months[2]	>2 years[3]	~3.5 years
TMB, HR (95% CI)				
<10 mut/Mb	0.73 (0.49–1.08)†		0.83 (0.54–1.29)‡	-
≥10 mut/Mb	0.73 (0.53–1.00)†		0.77 (0.46–1.30)‡	-
PD-L1, HR (95% CI)				
<1%	0.51 (0.30–0.89)	0.64 (0.46–0.90)	-	0.74 (0.54–1.01)
≥1%	0.87 (0.51–1.49)	0.69 (0.37–1.28)	-	0.81 (0.59–1.11)

*Treatment up to 35 cycles (~2 years). †Blood-based tumour mutational burden; ‡Tissue tumour mutational burden. CI, confidence interval; CP, carboplatin; EP, etoposide + platinum; ET, etoposide; HR, hazard ratio; mFU, median follow-up; NE, not estimable; OS, overall survival; TMB, tumour mutation burden.

1. Horn, et al. AACCR 2020 (Abs CT220); 2. Paz-Ares, et al. ESMO 2019 (Abs LBA89)
3. Goldman, et al. ESMO 2020 (Abs LBA86); 4. Rudin, et al. WCLC 2022 (Abs OA12.06)

Tumor heterogeneity (2021)

1



2

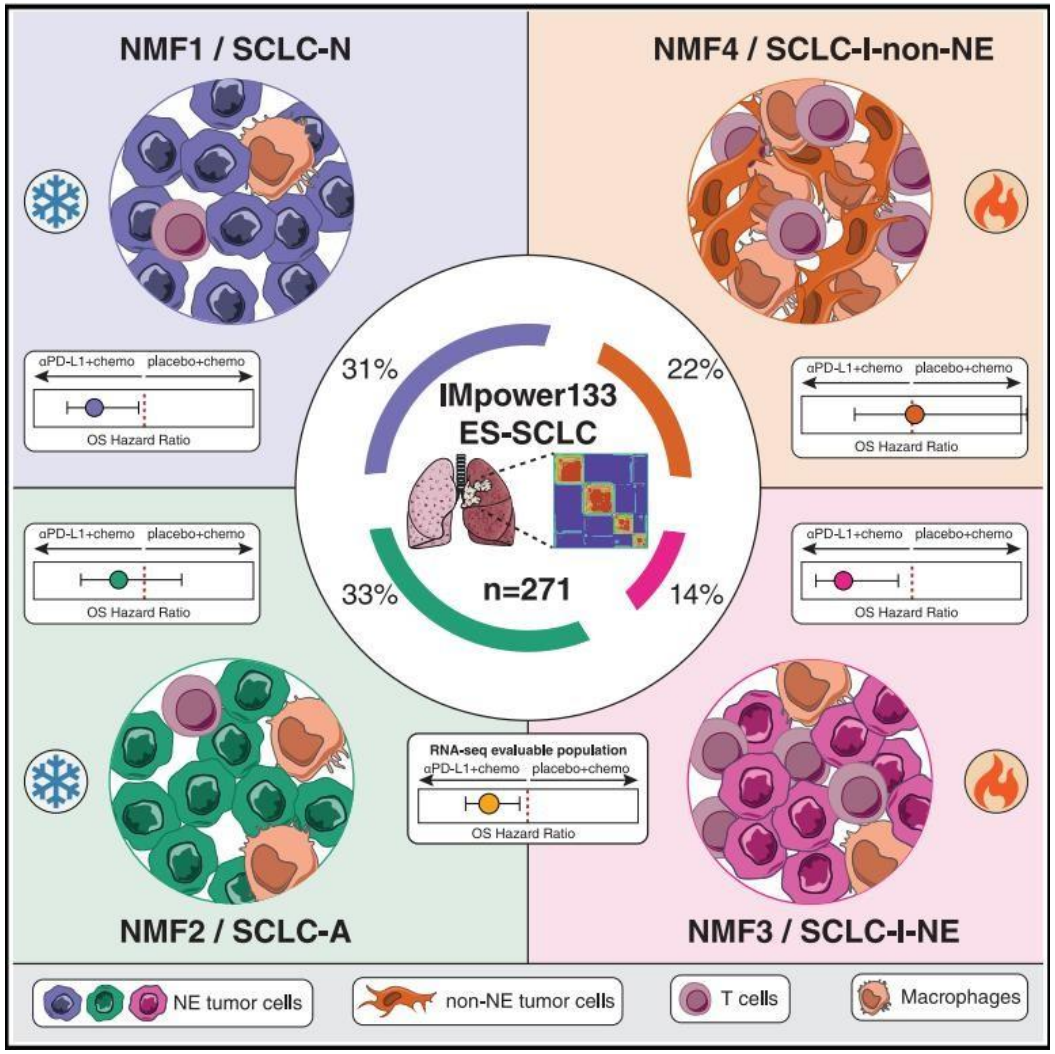
SCLC subtype	Neuroendocrine				Non-neuroendocrine			
	ASCL1 "classic", NE-high		NEUROD1 "variant", NE-low		POU2F3		YAP1	
	↑	↓	↑	↓	↑	↓	↑	↓
Marker expression	BCL-2 DLL3 CD56 CHGA E-cadherin EZH2 GRP1 IGFBP5 INSM1 LSD1 L-MYC NFIB RET TTF-1 SOX2 SYP	MYC CREBBP Notch	ANTXR1 AURKA MYC HES6 INSM1 LSH1 NCAM NFIB TrkB	E-cadherin TTF1	AURKA ASCL2 AVIL MYC E-cadherin GFI1B IGF-1R SOX9 TRPM5 CHAT ATM	IGFBP5 INSM1 TTF1 SLFN11	AJUBA AURKA CDK4/6 Integrins Laminin mTOR PD-L1 PLK RB1 SOX9 TAZ	MYC INSM1
Potential therapeutic approaches	BCL-2 inhibitors DLL3 inhibitors HDAC inhibitors LSD1 inhibitors		AURKA inhibitors c-MYC inhibitors ADI-PEG 20 Seneca Valley virus		PARP inhibitors IGF-1R inhibitors Nucleoside analogues		Immune-checkpoint inhibitors mTOR inhibitors PLK inhibitors CDK4/6 inhibitors	

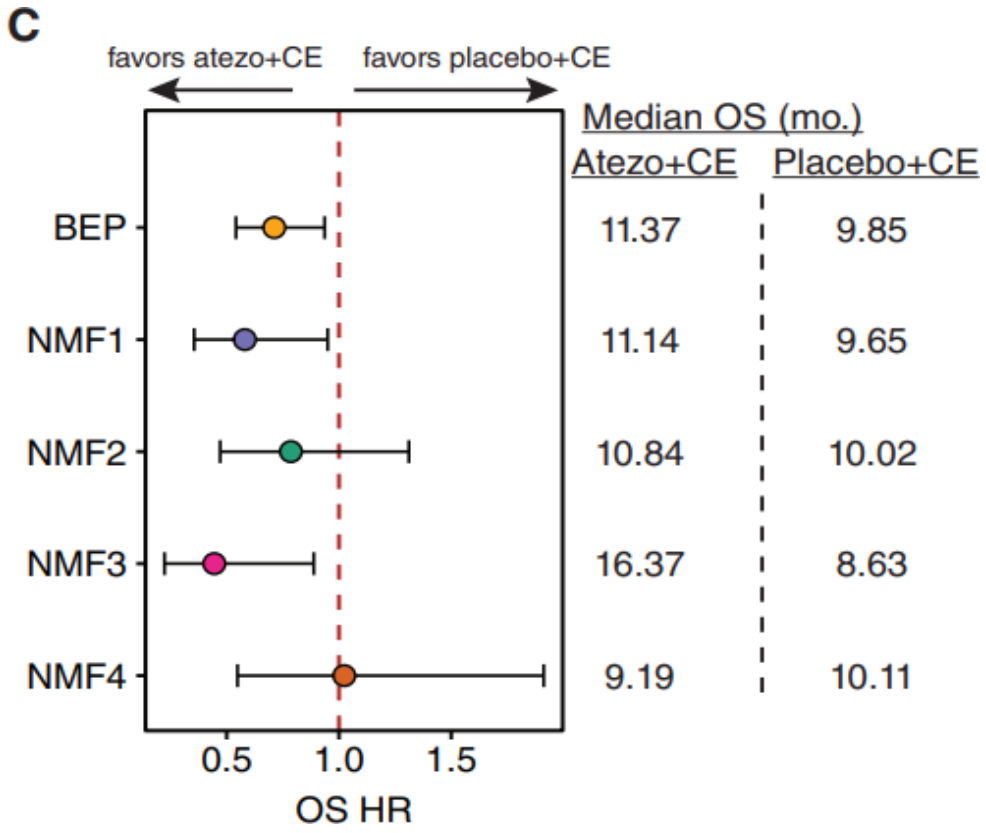
Loss of RB1 (Retinoblastoma 1); 75%-90% of patients [3]
Loss of TP53 (Tumor protein 53); nearly 100% [4]

1 Molecular Therapy: Oncolytics Vol. 20 March 2021
2 Solta et al. Molecular Cancer (2024) 23:41
3 George J, et al. Comprehensive genomic profles of small cell lung cancer. Nature. 2015;524:47–53.
4 Miller CW, et al. p53 mutations in human lung tumors. Cancer Res. 1992;52:1695–8.

Predictive marker

Transcriptional subtypes





Cancer Cell 42, 429–443, March 11, 2024

Treatment of SCLC

Extensive disease

Ist line Tx : ImmunoTx + Etoposide/platinum CTx → ImunoTx maintenance
IMPOWER 133, CASPIAN study

$2^{nd}/3^{rd}$ line Tx

SCLC SUBSEQUENT SYSTEMIC THERAPY (PS 0–2)[g]
Consider dose reduction or growth factor support for patients with PS 2

CHEMOTHERAPY-FREE INTERVAL (CTFI) >6 MONTHS

Preferred Regimens
- Clinical trial enrollment
- Re-treatment with platinum-based doublet[h,15-19]

Other Recommended Regimens
- Lurbinectedin[20,21]
- Topotecan oral (PO) or intravenous (IV)[22-25]
- Irinotecan[i,25,26]
- Tarlatamab-dlle[j,28]

CTFI ≤6 MONTHS

Preferred Regimens
- Clinical trial enrollment
- Lurbinectedin[20,21]
- Topotecan oral (PO) or intravenous (IV)[17,22-25]
- Irinotecan[i,25,26]
- Tarlatamab-dlle[j,28]
- Re-treatment with platinum-based doublet may be considered for CTFI 3–6 months[h,17-19]

Other Recommended Regimens
- Nivolumab[k] or pembrolizumab (if not previously treated with an ICI)[d,29-33]
- Paclitaxel[34,35]
- Temozolomide[36,37]
- Cyclophosphamide/doxorubicin/vincristine (CAV)[22]
- Docetaxel[38]
- Gemcitabine[27,39,40]
- Oral etoposide[41,42]

Lurbinectedin


Ecteinascidia turbinata

- Synthetic, marine-derived tetrahydroisoquinoline alkaloid
  - Analogue of DNA-damaging agent trabectedin

Drugs	Target	Mechanism of Action
Cisplatin, Carboplatin	DNA	- DNA 가닥 교차결합 형성 (Interstrand Crosslink) ; 복제 억제 및 세포 사멸 유도
Etoposide	Topoisomerase II	- Topoisomerase II 억제 → DNA 이중가닥 절단 유도 ; 세포 주기 G2/M기 정지 유발
Topotecan, Belotecan	Topoisomerase I	- Topoisomerase I 억제 → DNA 단일가닥 절단 유발 ; 복제 중 DNA 손상 증가
Lurbinectedin	**RNA Polymerase II**	**- DNA minor groove에 결합 → transcription 차단 – ; 전사 활성도가 높은 종양에서 선택적 apoptosis유도**

Lurbinectedin as second-line treatment for patients with small-cell lung cancer: a single-arm, open-label, phase 2 basket trial

José Trigo, Vivek Subbiah*, Benjamin Besse, Victor Moreno, Rafael López, María Angeles Sala, Solange Peters, Santiago Ponce, Cristian Fernández, Vicente Alfaro, Javier Gómez, Carmen Kahatt, Ali Zeaiter, Khalil Zaman, Valentina Boni, Jennifer Arrondeau, Maite Martínez, Jean-Pierre Delord, Ahmad Awada, Rebecca Kristeleit, Maria Eugenia Olmedo, Luciano Wannesson, Javier Valdivia, María Jesús Rubio, Antonio Anton, John Sarantopoulos, Sant P Chawla, Joaquín Mosquera-Martinez, Manolo D'Arcangelo, Armando Santoro, Victor M Villalobos, Jacob Sands, Luis Paz-Ares*

SCLC Patients

- PS 0-2
- One prior chemotherapy line
- Prior immunotherapy was allowed
- Active CNS mets excluded

Lurbinectedin 3.2 mg/m², 1h iv, q3wk

≥ 2 responses in first 15 patients* → **Enroll up to 100 patients**

* 5 confirmed responses observed in the first 15 treated patients

PRIMARY OBJECTIVE : *ORR by RECIST V.1.1*

Data cut-off: January 15th 2019

Statistical assumptions for SCLC cohort

- **Null hypothesis :** ≤15% get a response ($p \leq 0.15$)
- **Alternative hypothesis :** ≥30% get a response ($p \geq 0.30$)
- **Statistical power** 95%
- **≥ 23% of confirmed responses needed to reject the null hypothesis**

Trigo. Lancet Oncol. 2020;21:645.

Lurbinectedin as Single Agent in Second Line SCLC

	All patients (n=105)	Chemotherapy-free interval <90 days (n=45)	Chemotherapy-free interval ≥90 days (n=60)
RECIST responses			
Complete response	0	0	0
Partial response	37 (35%)	10 (22%)	27 (45%)
Stable disease*	35 (33%)	13 (29%)	22 (37%)
Progressive disease	28 (27%)	18 (40%)	10 (17%)
Not evaluable†	5 (5%)	4 (9%)	1 (2%)
Overall response, % (95% CI)	35·2% (26·2–45·2)	22·2% (11·2–37·1)	45·0% (32·1–58·4)
Disease control, % (95% CI)‡	68·6% (58·8–77·3)	51·1% (35·8–66·3)	81·7% (69·6–90·5)
Duration of response			
Disease progression, relapse, or death events in responding patients, n/N (%)	29/37 (78%)	9/10 (90%)	20/27 (74%)
Median duration of response, months	5·3 (4·1–6·4)	4·7 (2·6–5·6)	6·2 (3·5–7·3)
Patients still responding at 6 months	43·0% (25·6–60·5)	11·7% (0·0–33·1)	55·3% (34·5–76·0)
Progression-free survival			
Progression-free survival events, n (%)	90 (86%)	41 (91%)	49 (82%)
Median progression-free survival, months (95% CI)	3·5 (2·6–4·3)	2·6 (1·3–3·9)	4·6 (2·8–6·5)
4-month progression-free survival (95%CI)	46·6% (36·7–56·5)	29·1% (15·3–42·8)	59·9% (47·1–72·7)
6-month progression-free survival (95% CI)	32·9% (23·3–42·5)	18·8% (6·8–30·9)	43·5% (30·1–56·9)
Overall survival			
Deaths	66 (63%)	37 (82%)	29 (48%)
Median overall survival, months (95% CI)	9·3 (6·3–11·8)	5·0 (4·1–6·3)	11·9 (9·7–16·2)
6-month overall survival (95%CI)	67·1% (57·6–76·7)	45·8% (30·4–61·3)	83·6% (73·7–93·5)
12-month overall survival (95% CI)	34·2% (23·2–45·1)	15·9% (3·6–28·2)	48·3% (32·5–64·1)

RECIST=Response Evaluation Criteria in Solid Tumors. *Includes five patients with partial response not confirmed. †Five patients were not evaluable because they had no radiological assessment during treatment due to early death from malignant disease (n=2), symptomatic deterioration because of disease progression (n=2), and patient refusal (n=1). ‡Partial response or stable disease.

Table 2: **Overall efficacy of lurbinectedin treatment by investigator assessment and subgroup analyses by chemotherapy-free interval**

Trigo. Lancet Oncol. 2020;21:645.

2nd -Line CTx Regimens for SCLC

Author (y)	Regimen	No. of Patients	Overall Response Rate (%)	Median Survival	1-Year Survival Rate (%)
Von Pawel et al. (1999)	Topotecan	107	24.3	25 wk	14.2
	CAV	104	18.3	18.3 wk	14.4
O'Brien et al. (2006)	Topotecan	71	NR	25.5 wk	NR
	Best supportive care	70	7	13.9 wk	NR
Eckardt et al. (2003)	Topotecan (IV)	151	21.9	35 wk	29
	Topotecan (PO)	153	18.3	33 wk	33
Jotte et al. (2011)	Topotecan (IV)	424	31	7.5 mo	28
	Amrubicin	213	17	7.8 mo	25

[a]$p < 0.05$. *CAV*, cyclophosphamide, doxorubicin, and vincristine; *IV*, intravenous; *NR*, not reported; *PO*, oral.

Lurbinectedin as Single Agent in Second Line SCLC

	All patients (n=105)	Chemotherapy-free interval <90 days (n=45)	Chemotherapy-free interval ≥90 days (n=60)
RECIST responses			
Complete response	0	0	0
Partial response	37 (35%)	10 (22%)	27 (45%)
Stable disease*	35 (33%)	13 (29%)	22 (37%)
Progressive disease	28 (27%)	18 (40%)	10 (17%)
Not evaluable†	5 (5%)	4 (9%)	1 (2%)
Overall response, % (95% CI)	35·2% (26·2–45·2)	22·2% (11·2–37·1)	45·0% (32·1–58·4)
Disease control, % (95% CI)‡	68·6% (58·8–77·3)	51·1% (35·8–66·3)	81·7% (69·6–90·5)
Duration of response			
Disease progression, relapse, or death events in responding patients, n/N (%)	29/37 (78%)	9/10 (90%)	20/27 (74%)
Median duration of response, months	5·3 (4·1–6·4)	4·7 (2·6–5·6)	6·2 (3·5–7·3)
Patients still responding at 6 months	43·0% (25·6–60·5)	11·7% (0·0–33·1)	55·3% (34·5–76·0)
Progression-free survival			
Progression-free survival events, n (%)	90 (86%)	41 (91%)	49 (82%)
Median progression-free survival, months (95% CI)	3·5 (2·6–4·3)	2·6 (1·3–3·9)	4·6 (2·8–6·5)
4-month progression-free survival (95%CI)	46·6% (36·7–56·5)	29·1% (15·3–42·8)	59·9% (47·1–72·7)
6-month progression-free survival (95% CI)	32·9% (23·3–42·5)	18·8% (6·8–30·9)	43·5% (30·1–56·9)
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RECIST=Response Evaluation Criteria in Solid Tumors. *Includes five patients with partial response not confirmed. †Five patients were not evaluable because they had no radiological assessment during treatment due to early death from malignant disease (n=2), symptomatic deterioration because of disease progression (n=2), and patient refusal (n=1). ‡Partial response or stable disease.

Table 2: **Overall efficacy of lurbinectedin treatment by investigator assessment and subgroup analyses by chemotherapy-free interval**

Trigo. Lancet Oncol. 2020;21:645.

Platinum re-challenge vs. Lurbinectedin

Lung Cancer 150 (2020): 90-96

	CTFI ≥ 90 days									CTFI ≥ 180 days	
	Platinum re-challenge								Lurbinectedin	Platinum re-challenge	Lurbinectedin
Reference	Korkmaz (2013) [5]	Inoue (2015) [6]	Wakuda (2015) [7]	Genestreti (2015) [8]	Shiozawa (2018) [9]	Naito (2018) [10]	Wakuda (2019) [11]	Monnet (2019) [12]	Trigo (2020) [19]	Wakuda (2015) [7]	Current analysis
STUDY DESIGN	Retrospective analysis	Phase II randomized	Retrospective analysis	Retrospective analysis	Retrospective analysis	Retrospective analysis	Retrospective analysis	Phase III randomized	Phase II single-arm	Retrospective analysis	Phase II single-arm
(n)	(n = 33)	(n = 30)	(n = 19)	(n = 112)	(n = 20)	(n = 67)	(n = 27)	(n = 81)	(n = 60)	(n = 11)	(n = 20)
Median CTFI (range)	NA	60 % CTFI >180 days	7.1 (3.1–39.2)	7.9 (3.0–39.5)	3.8 (3.0–13.2)	5.9 (3.1–50.0)	6.6 (3.1–38.7)	5.3 (4.7–5.8)	4.8 (3.0–16.1)	8.8 (6.0–38.7)	7.5 (6.0–16.1)
Age (years), median (range)	58 (NA)	67 (45–80)	69 (51–83)	64 (40–83)	65 (52–84)	NA	66 (51–73)	64 (NA)	59 (44–79)	69 (52–79)	57 (49–75)
Response first line %	NA	NA	95 %	98 %	NA	NA	98 %	NA	85 %	100 %	85 %
Limited disease, %	39 %	60 %	63 %	44 %	55 %	49 %	44 %	NA	42 %	73 %	65 %
ECOG PS 0–1, %	82 %	93 %	95 %	87 %	90 %	85 %	89 %	94 %	95 %	91 %	95 %
EFFICACY OUTCOMES											
ORR, % (95 %CI)	55 (NA)	43 (28–58)	37 (19–59)	45 (NA)	50 (NA)	52 (NA)	48 (NA)	49 (NA)	45 (32–58)	46 (21–72)	60 (36–87)
Disease control rate, % (95 %CI)	NA	80 (68–92)	84 (NA)	64 (NA)	80 (NA)	82 (NA)	74 (NA)	86 (NA)	82 (70–91)	73 (NA)	95 (75–100)
PFS (months), median (95 %CI)	6.2 (NA)	5.1 (NA)	5.6 (NA)	5.5 (4.4–6.3)	4.5 (3.5–5.4)	5.1 (4.3–5.4)	5.5 (3.4–6.1)	4.7 (3.9–5.5)	4·6 (2.8–6.5)	7.8 (NA)	4.6 (2.6–7.3)
OS (months), median (95 %CI)	11.4 (NA)	14.3 (NA)	14.4 (NA)	7.9 (6.9–9.7)	10.5 (7.9–13.0)	10.8 (8.7–14.5)	14.2 (6.4–25.6)	7.5 (5.4–9.5)	11.9 (9.7–16.2)	15.7 (NA)	16.2 (9.6-nr)
SAFETY OUTCOMES											
Primary G-CSF use	NA	No	NA	NA	NA	NA	NA	Yes	No	NA	No
Grade 3/4 neutropenia, %	NA	73 %	94 %	NA	65 %	NA	85 %	23 %	46 %	NA	45 %
Febrile neutropenia, %	NA	0%	16 %	NA	15 %	NA	19 %	6%	5%	NA	0%
Grade 3/4 thrombocytopenia, %	NA	27 %	26 %	NA	10 %	NA	37 %	41 %	7%	NA	10 %
Grade 3/4 fatigue, %	NA	3%	0%	NA	0%	NA	11 %	7%	7%	NA	10 %

CI, confidence interval; CTFI, chemotherapy-free interval; ECOG PS, Eastern Cooperative Oncology Group performance status; PFS, progression-free survival; NA, not available; nr, not reached (upper level); ORR, overall response rate; OS, overall survival.

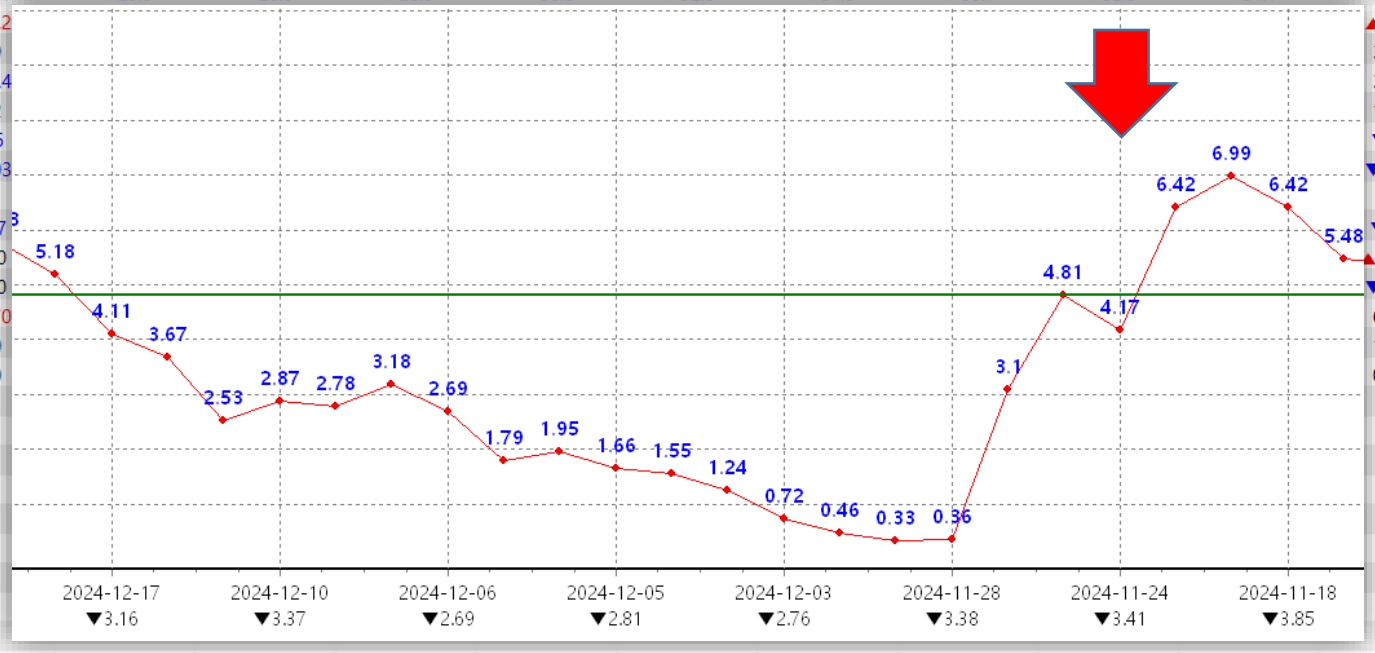
Lurbinectedin as Single Agent in Second Line SCLC

	Grade 1–2	Grade 3	Grade 4
Haematological abnormalities (regardless of relation to study drug)*			
Anaemia	91 (87%)	9 (9%)	0
Leucopenia	53 (50%)	20 (19%)	10 (10%)
Neutropenia	27 (26%)	22 (21%)	26 (25%)
Thrombocytopenia	39 (37%)	3 (3%)	4 (4%)
Biochemical abnormalities (regardless of relation to study drug)*			
Creatinine†	86/104 (83%)	0	0
Alanine aminotransferase	69/103 (67%)	5/103 (5%)	0
γ-glutamyl transferase	52/103 (50%)	13/103 (13%)	2/103 (2%)
Aspartate aminotransferase	44/103 (43%)	2/103 (2%)	0
Alkaline phosphatase	31/103 (30%)	3/103 (3%)	0
Treatment-related adverse events			
Fatigue	54 (51%)	7 (7%)	0
Nausea	34 (32%)	0	0
Decreased appetite	22 (21%)	0	0
Vomiting	19 (18%)	0	0
Diarrhoea	13 (14%)	1 (1%)	0
Febrile neutropenia	0	2 (2%)	3 (3%)
Pneumonia	0	2 (2%)	0
Skin ulcer	0	1 (1%)	0

Table 3: **Most common NCI-CTCAE laboratory abnormalities and treatment-related adverse events**

Trigo. Lancet Oncol. 2020;21:645.

날짜정렬 ○ 정배열(→) ● 역배열(←)				IMPM 2024-12-04	IMPM 2024-12-04	IMPM 2024-12-03	IMPM 2024-12-02	IMPM 2024-11-30	IMPM 2024-11-28	IMPM 2024-11-26	IMPM 2024-11-25	IMPM 2024-11-24	IMPM 2024-11-22	IMPM 2024-11-22	20
검 사 명	단위	하한	상한	16:07	05:47	11:50	08:40	08:54	09:13	11:48	09:09	06:36	16:06[S2]	09:51	
WBC	x10³/㎕	4.8	10.8	▼1.55	▼1.24	▼0.72	▼0.46	▼0.33	▼0.36	▼3.10	4.81	▼4.17	6.42	6.99	
RBC	x100³/㎕	4.7	6.1	▼2.51	▼2.67	▼2.76	▼2.88	▼3.16	▼3.38	▼3.55	▼3.64	▼3.41	▼3.61	▼3.77	
Hb	g/dl	13	16.5	▼7.5	▼8.3	▼8.5	▼8.8	▼9.8	▼10.5	▼11.1	▼11.4	▼10.6	▼11.2	▼11.9	
Hct	%	42	49	▼23.9	▼25.8	▼26.0	▼28.3	▼30.8	▼32.8	▼34.3	▼35.7	▼32.0	▼34.1	▼36.1	
MCV	fL	80	94	▲95.2										▲95.8	
MCH	pg	27	32	29.9										31.6	
MCHC	g/dl	33	37	▼31.4										33.0	
RDW	%	11.5	14.5	13.2										13.1	
Platelet	x10³/㎕	130	450	▼35										▼89	
PCT	%	0.235	0.991	▼0.03										▼0.08	
MPV	fL	7.4	10.4	9.6										9.1	
PDW	fl	12	16.5	▼9.7										▼9.5	
Neutrophil %	%	50	75	65.20										▲84.00	
Lymph %	%	20	44	23.20										▼7.30	
Mono %	%	2	9	▲9.70										6.70	
Eosino %	%		5	1.30										1.70	
Basoph %	%		2	0.60										0.30	
Blast %	%		0												
Promyelo %	%		0												
Myelo %	%		0												
Metamyelo %	%		0												
Band %	%														
Immature lymp	%		0												
Immature cell ?	%		0												
Atypical lymph	%														
N RBC/100WBC	/100WBC														
Lymph #	x10³/㎕	1.0	4.8	▼0.36	▼0.44	▼0.33	▼0.30	▼0.28	▼0.21	▼0.34	▼0.40	▼0.33	▼0.51	▼0.51	
Mono #	x10³/㎕	0	0.8	0.15	0.09	0.07	0.07	0.03	0.02	0.06	0.09	0.21	0.53	0.47	
Neutrophil #	x10³/㎕	1.8	7.8	▼1.01	▼0.68	▼0.28	▼0.07	▼0.01	▼0.11	2.65	4.21	3.59	5.23	5.87	
Eosinophil #	x10³/㎕	0	0.45	0.02	0.03	0.03	0.02	0.01	0.02	0.04	0.09	0.03	0.14	0.12	
Basophil #	x10³/㎕	0	0.2	0.01	0.00	0.01	0.00	0.00	0.00	0.01	0.02	0.01	0.01	0.02	
Atypical cell %			0												
ESR	mm/hr		9		▲72		▲90		▲109		▲45			▲43	



ZEPZELCA™ dosing and administration[1]

- Recommended dose reductions for adverse reactions

Dose	1st Dose Reduction	2nd Dose Reduction	3rd Dose Reduction
3.2 mg/m² →	2.6 mg/m² →	2.0 mg/m²	**Stop***

*Permanently discontinue ZEPZELCA if 2 mg/m² is not tolerated or if a dose delay greater than 2 weeks is required.

Dose modifications for ZEPZELCA for adverse reactions

Withold ZEPZELCA if any of the following adverse reactions occurs, :

- **Neutropenia**[a], Grade[b] 4 (neutrophil count <500 cells/mm³), or any grade of febrile neutropenia
- **Thrombocytopenia**, Grade 3 (Platelet count 25,000 – 50,000 cells/mm3) with bleeding or Grade 4 (Platelet count <25,000 cells/mm³)
- **Hepatotoxicity and other reverse reactions**, Grade 2 or Grade ≥3

Resume treatment at reduced dose once symptoms have improved (see SmPC for specifications)

Lurbinectedin/doxorubicin *versus* CAV or topotecan in relapsed SCLC patients: Phase III randomized ATLANTIS trial

Negative results…

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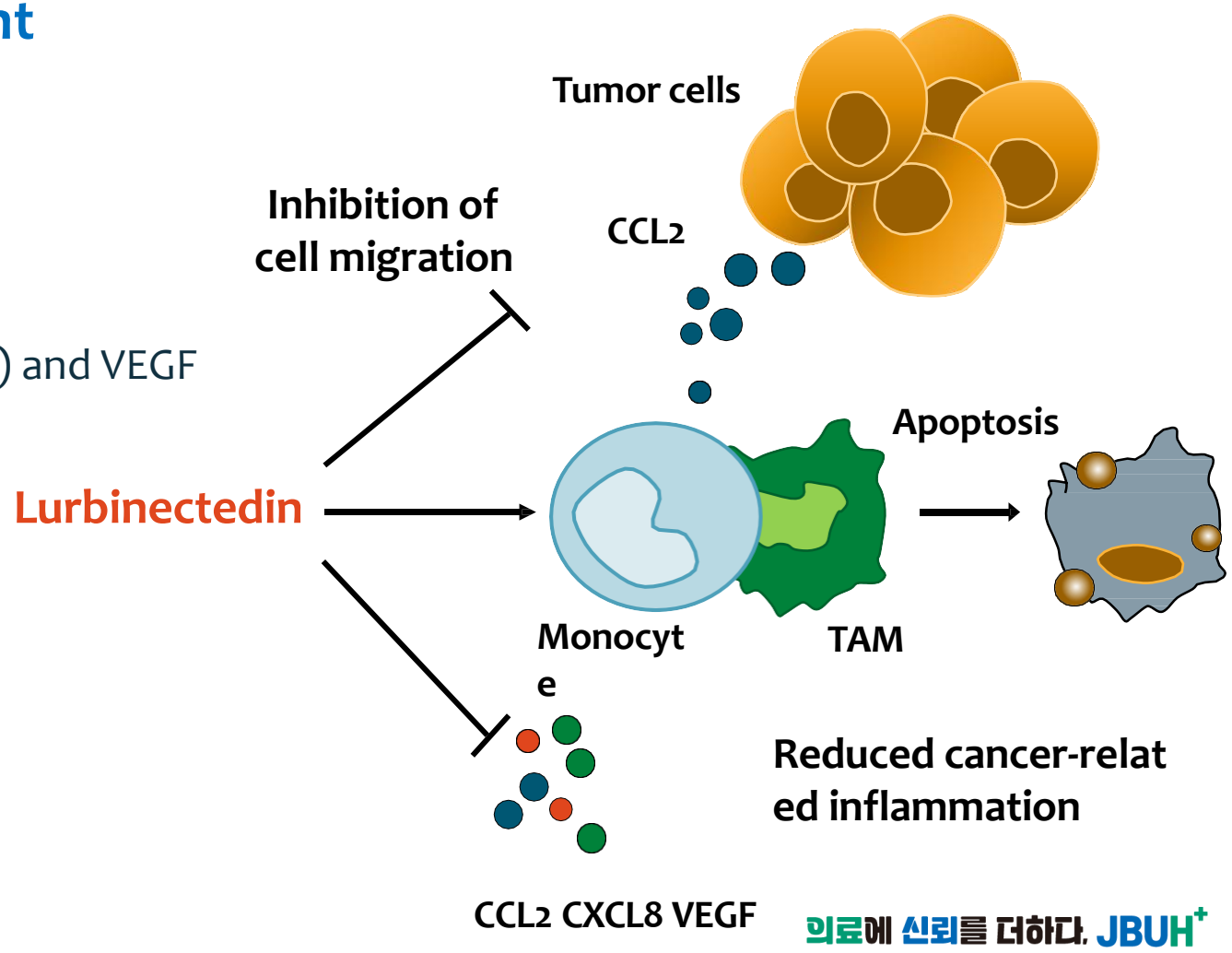
Lurbinectedin

- **Effects on the tumor microenviroment**

Based on a preclinical study:

- Induce apoptosis in tumor-associated macrophapes
- Reduce macrophage infiltration
- Reduce inflammatory chemokines (CCL2 and CXCLB) and VEGF



- **Lurbinectedin + immunotherapies (multiple different trials)**

  eg, IMforte phase 3 trial (NCT05091567) evaluating lurbinectedin + atezolizumab in adults with ES-SCLC following induction therapy with carboplatin, etoposide, and atezolizumab; primary objective is to determine the ability of this new combination to improve outcomes for patients with ES-SCLC compared with standard-of-care first-line maintenance as measured by PFS and OS

Phase 3 Open-Label Study of Maintenance Lurbinectedin in Combination with Atezolizumab compared with Atezolizumab in participants with ES-SCLC (IMforte Trial)

Last Update Posted ⓘ 2024-10-08

Madrid, October 15th, 2024.- PharmaMar (MSE: PHM) and its partner Jazz Pharmaceuticals plc (Nasdaq: JAZZ) have announced today positive top-line results from the Phase 3 clinical trial evaluating Zepzelca® (lurbinectedin) in combination with the PD-L1 inhibitor atezolizumab (Tecentriq®) compared to atezolizumab alone when administered as a maintenance treatment for adults with extensive-stage Small Cell Lung Cancer (ES-SCLC) following induction therapy with carboplatin, etoposide and atezolizumab. The combination of lurbinectedin and atezolizumab demonstrated a statistically significant improvement in the primary endpoints of overall survival (OS) and progression-free survival (PFS), as assessed by an independent review facility (IRF), compared to treatment with atezolizumab alone.

- Enrollment (Estimated) : 690
- 8 centers in Korea are participating in this clinical trial

Lurbinectedin plus pembrolizumab in relapsed small cell lung cancer (SCLC): the phase I/II LUPER study

Journal of Thoracic Oncology

RELAPSED SCLC PATIENTS

- Progressing to first-line platinum-based chemotherapy
- ECOG PS 0-1
- No prior immunotherapy
- Asymptomatic CNS metastasis

GOAL: To evaluate the efficacy and safety of lurbinectedin combined with pembrolizumab in patients with relapsed SCLC, aiming to prevent early disease progression and achieve durable responses

TRIAL OVERVIEW

Phase I
Dose Escalation (3+3 design)

N = 3-6 patients per dose

Lurbinectedin 2.4 mg/m² (starting dose)
+
Pembrolizumab 200 mg

ENDPOINTS	
PRIMARY	**SECONDARY**
• RP2D and MTD of lurbinectedin combined with pembrolizumab	• Safety as per NCI-CTCAE 5.0 • Preliminary efficacy by RECIST 1.1

Phase II
Dose Expansion

N ≈ 30 patients

Lurbinectedin RP2D
+
Pembrolizumab 200 mg

ENDPOINTS	
PRIMARY	**SECONDARY**
• ORR as per RECIST 1.1	• Safety as per NCI-CTCAE 5.0 • CBR, DoR, PFS, and OS • PK and PGx

RESULTS

Phase I

RP2D

3.2 mg/m² Lurbinectedin
+
200 mg Pembrolizumab

Phase II

N=28 patients

Efficacy

	Platinum-resistant	Platinum-sensitive	Overall
ORR	37.5% (95% CI 12.8;64.9)	57.1% (95% CI 28.9;82.3	46.4% (95% CI 27.5;66.1)
DoR	4.4 mo (95% CI 0.9;NA)	11.9 mo (95% CI 2.8;NA)	7.8 mo (95% CI 2.8;19.1
PFS	2.8 mo (95% CI 1.2;5.6)	8.0 mo (95% CI 2.7;15.2	4.6 mo (95% CI 2.7;6.0)
OS	7.1 mo (95% CI 1.4;11.1)	15.7 mo (95% CI 7.7;NA)	10.5 mo (95% CI 6.9;17.6)

Safety

TRAEs	Any grade	Grade ≥3
Any	28 (100%)	23 (82.1%)
Neutropenia	19 (67.9%)	13 (46.4%)
Fatigue	21 (75.0%)	2 (7.1%)

CONCLUSION: Lurbinectedin plus pembrolizumab showed promising efficacy in relapsed SCLC, particularly for platinum-sensitive patients, with a known and manageable safety profile.

Calles A, et al. J Thorac Onc. 2025

Ongoing Randomized Phase II or III Trials of Lurbinectedin

Trial	Phase	Planned N	Population	Treatment Arms	Primary Endpoint(s)
LAGOON (NCT05153239)	III	705	Relapsed ES-SCLC after 1 prior platinum-based regimen with CTFI ≥30 days	2L+ lurbinectedin **vs** lurbinectedin + irinotecan **vs** irinotecan or topotecan	OS
LURBIMUNE (NCT05572476)	II	82	Recurrent ES-SCLC after 1 prior platinum-based regimen* with CTFI ≥90 days†	Lurbinectedin + durvalumab **vs** carboplatin/etoposide	6-mo PFS rate by BCRR

*Platinum sensitive. †1L platinum/etoposide + PD-L1 inhibitor required.

ClinicalTrials.gov.

SCLC SUBSEQUENT SYSTEMIC THERAPY (PS 0–2)[g] Consider dose reduction or growth factor support for patients with PS 2
CHEMOTHERAPY-FREE INTERVAL (CTFI) >6 MONTHS
Preferred Regimens • Clinical trial enrollment • Re-treatment with platinum-based doublet[h,15-19] **Other Recommended Regimens** • Lurbinectedin[20,21] • Topotecan oral (PO) or intravenous (IV)[22-25] • Irinotecan[i,25,26] • Tarlatamab-dlle[j,28]
CTFI ≤6 MONTHS
Preferred Regimens • Clinical trial enrollment • Lurbinectedin[20,21] • Topotecan oral (PO) or intravenous (IV)[17,22-25] • Irinotecan[i,25,26] • Tarlatamab-dlle[j,28] • Re-treatment with platinum-based doublet may be considered for CTFI 3–6 months[h,17-19] **Other Recommended Regimens** • Nivolumab[k] or pembrolizumab (if not previously treated with an ICI)[d,29-33] • Paclitaxel[34,35] • Temozolomide[36,37] • Cyclophosphamide/doxorubicin/vincristine (CAV)[22] • Docetaxel[38] • Gemcitabine[27,39,40] • Oral etoposide[41,42]

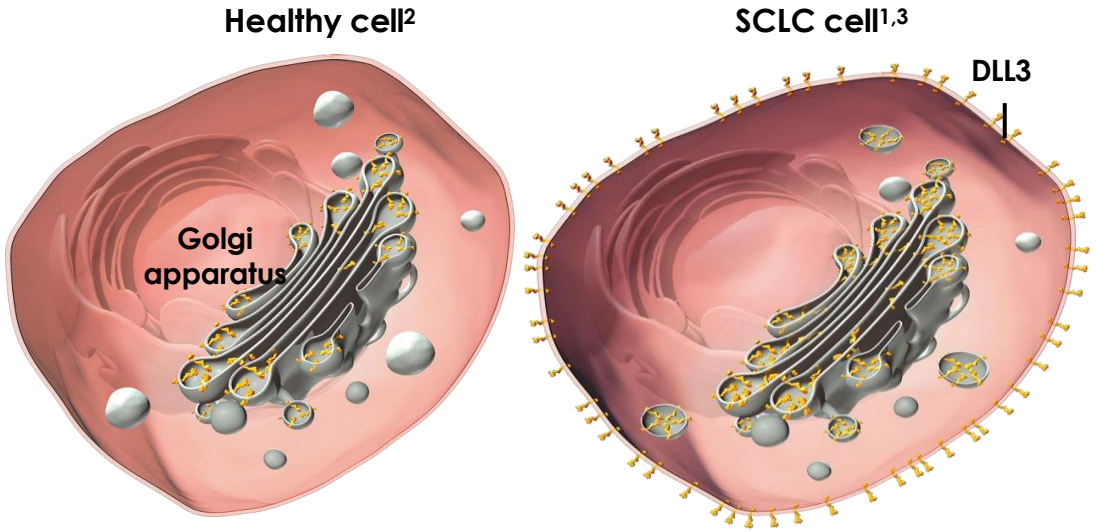
Selected Targets and Agents Studied for SCLC

Target	Agent	Phase	Result	Comment
VEGF-A	Bevacizumab	Ⅲ	Negative	In combination with cisplatin + etoposide
				Statistically significant improvement in PFS but not OS
VEGFR-Ⅰ-Ⅲ	Cediranib	Ⅱ	Negative	
VEGFR, PDGFR, Raf-1	Sorafenib, thalidomide	Ⅱ, Ⅲ	Negative	
VEGFR, PDGFR, Flt-3, RET, Kit	Sunitinib	Ⅱ, Ⅲ	Negative	
VEGF-A, B	Aflibercept	Ⅱ	Negative	
	NGR-hTNF	Ⅱ	Negative	
VEGF, EGFR	Vandetanib	Ⅱ	Negative	
cKit	Imatinib	Ⅱ	Negative	cKit expression required
Src	Dasatinib, Saracatinib	Ⅱ	Negative	
mTOR	Everolimus, temsirolimus	Ⅱ	Negative	
EGFR	Gefitinib	Ⅱ	Negative	Responses in EGFR MT patients
BCl-2	Oblimersen, navitoclax, obatoclax, AT101	Ⅰ/Ⅱ	Negative	
RAS	R115777	Ⅱ	Negative	
Aurora A kinase	Alisertib	Ⅰ/Ⅱ	21% PR	Relapsed/refractory disease
HDAC	Romidepsin, panobinostat	Ⅱ	Negative	
PARP	Veliparib	Ⅰ	Acceptable safety profile	In combination with cisplatin + etoposide in newly diagnosed ED-SCLC

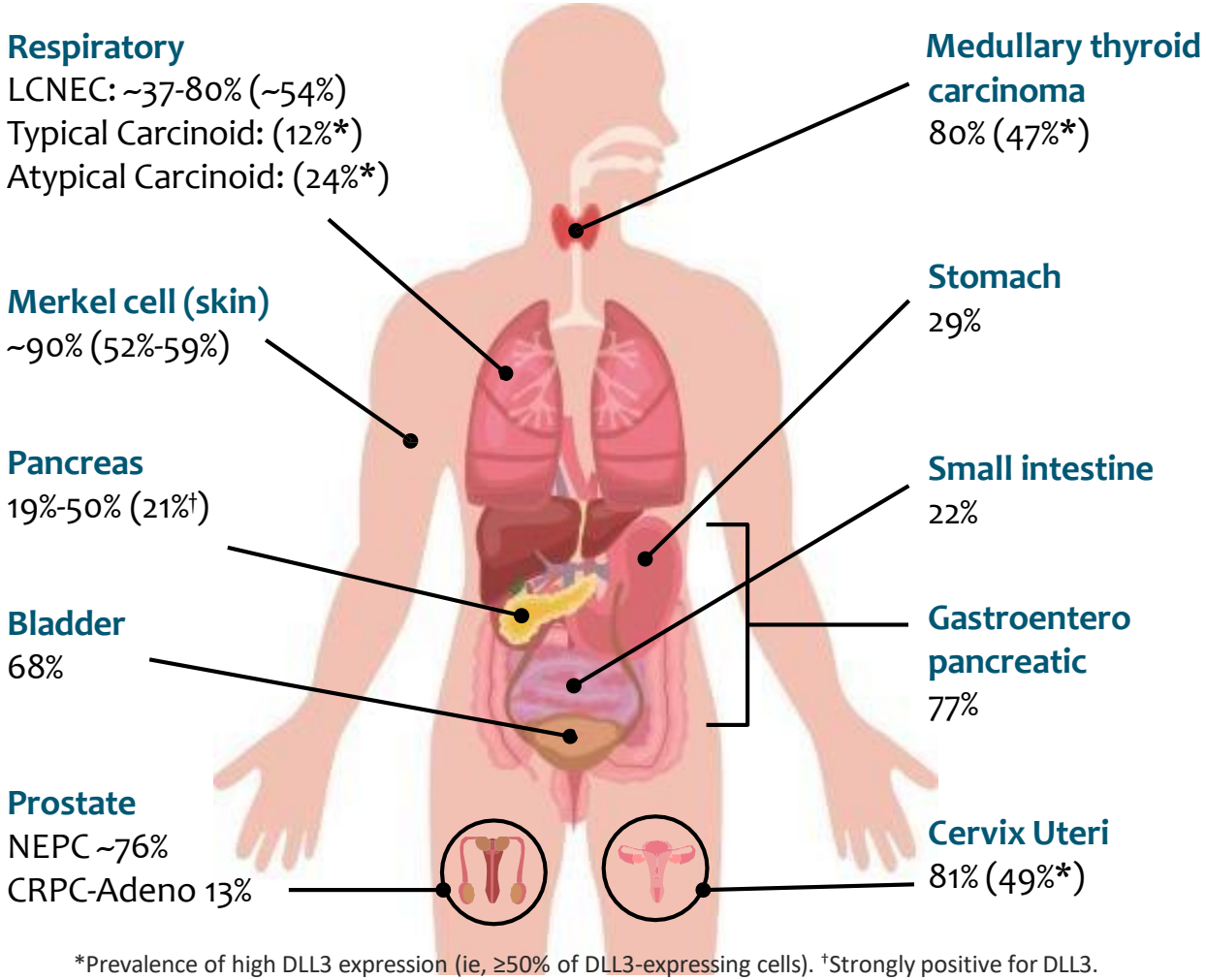
BCl-2, B-cell CLL/lymphoma 2; *ED-SCLC*, extensive-stage disease small cell lung cancer; *EGFR*, epidermal growth factor receptor; *Flt-3*, Fms-like tyrosine kinase 3; *HDAC*, histone deacetylase; *MT*, mutated; *mTOR*, mammalian target of rapamycin; *NGR-hTNF*, CNGRC-human Tumor Necrosis Factor-alfa fusion protein; *OS*, overall survival; *PARP*, poly(ADP) ribose polymerase; *PDGFR*, platelet-derived growth factor receptor; *PFS*, progression-free survival; *PR*, partial response; *RAS*, rat sarcoma gene; *RET*, rearranged during transfection proto-oncogene; *VEGF*, vascular endothelial growth factor; *VEGFR*, VEGF receptor.

Rationale: DLL3 Expression in Neuroendocrine Cancers

- DLL3, an inhibitory Notch signaling protein, is expressed on cancer cells in ~ 85%–96% o f patients with SCLC[1-4]
- DLL3 is typically localized intracellularly in healthy cells but may be abnormally expre ssed on the surface of SCLC cells[1,2,5]



Representative Prevalence of DLL3 in NEN



*Prevalence of high DLL3 expression (ie, ≥50% of DLL3-expressing cells). †Strongly positive for DLL3.

BiTE, bispecific T cell engager; **DLL3,** delta-like ligand 3; **SCLC,** small cell lung cancer.

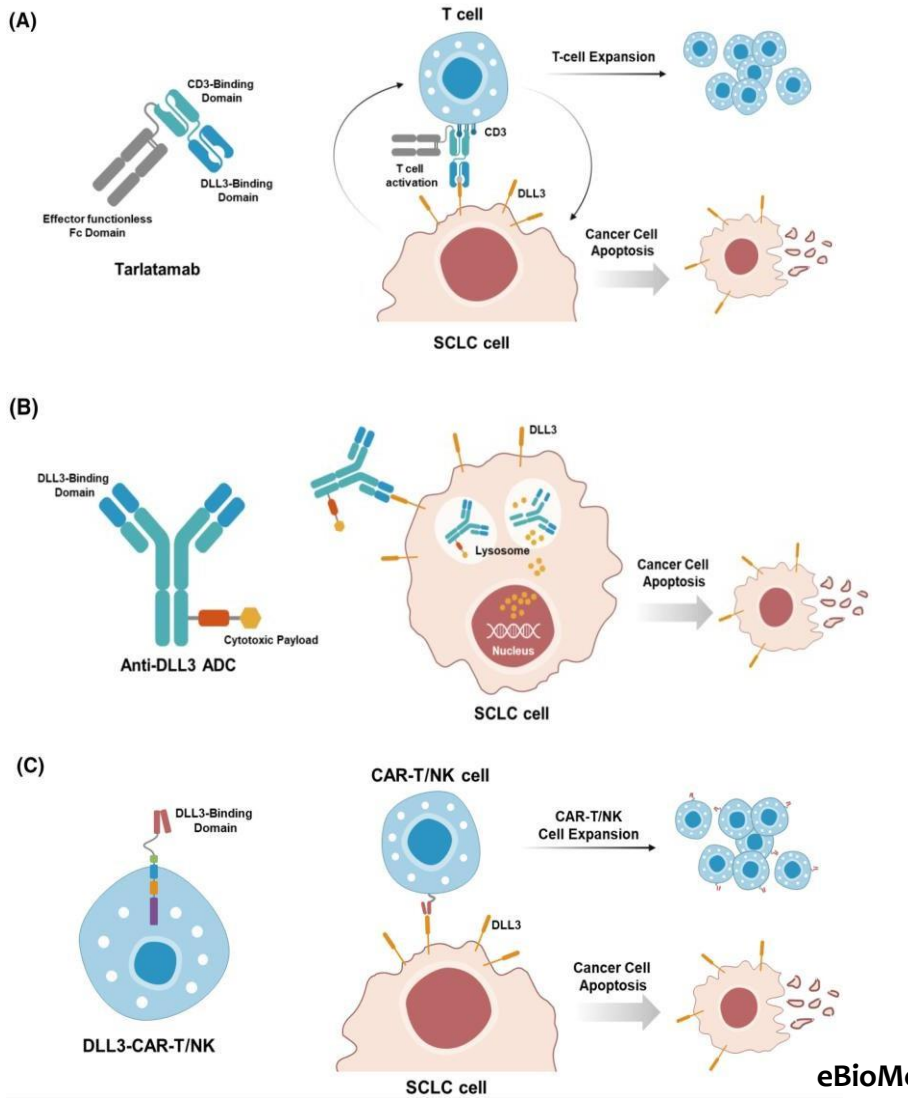
1. Sabari JK, et al. *Nat Rev Clin Oncol*. 2017;14:549-561. 2. Leonetti A, et al. *Cell Oncol (Dordr)*. 2019;42:261-273. 3. Rojo F, et al. *Lung Cancer*. 2020;147:237-243. 4. Ahn MJ, et al. *N Engl J Med*. 2023;389:2063-2075. 5. Saunders LR, et al. *Sci Transl Med*. 2015;7:302ra136. 6. Einsele H, et al. *Cancer*. 2020;126:3192-3201.

DLL3 targeting in SCLC

T cell engager
- CD3 in T cell
- DLL3 in SCLC
- Tarlatamab, BI 764532, MK-6070

Anti-DLL3 Antibody drug conjugate(ADC)
-DLL-3 specific ADC – linker – Drug
- Rova-T (PBD, pyrolobenodizepin)

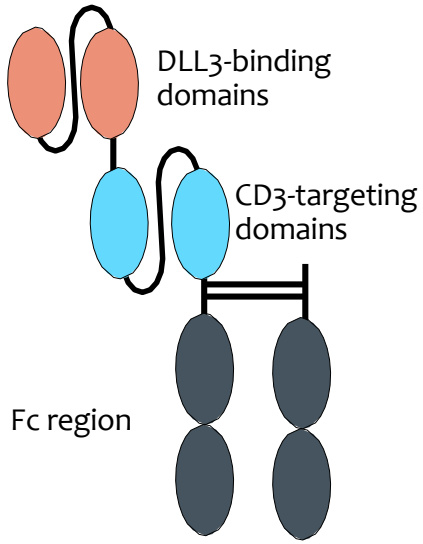
CAR-T/NK cell
- CAR with DLL-3 binding domain
- AMG 119, DLL-CAR-NK-92 cells



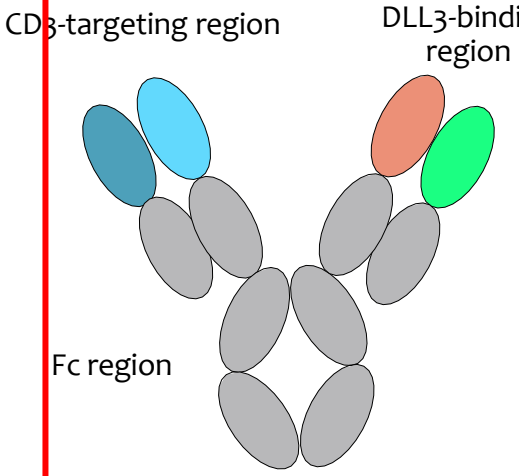
eBioMedicine 2024;102: 105062

DLL3 T-Cell Engagers in Development

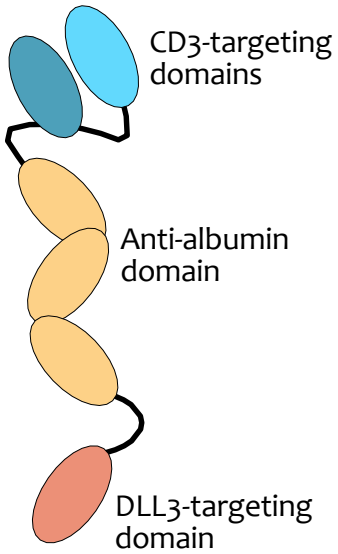
Tarlatamab



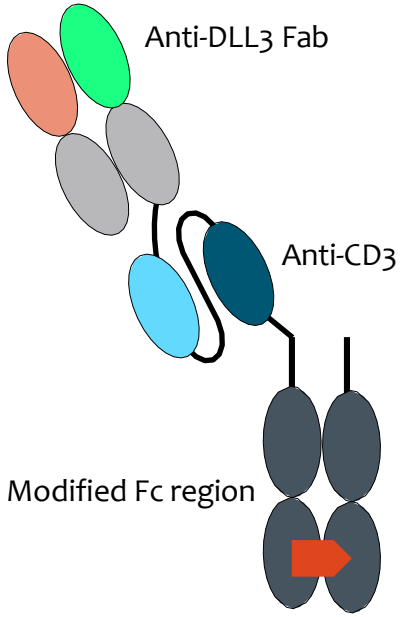
BI 764532



MK-6070 (HPN 328)



QLS31904



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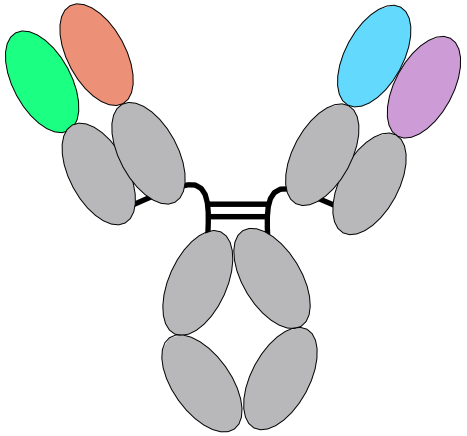
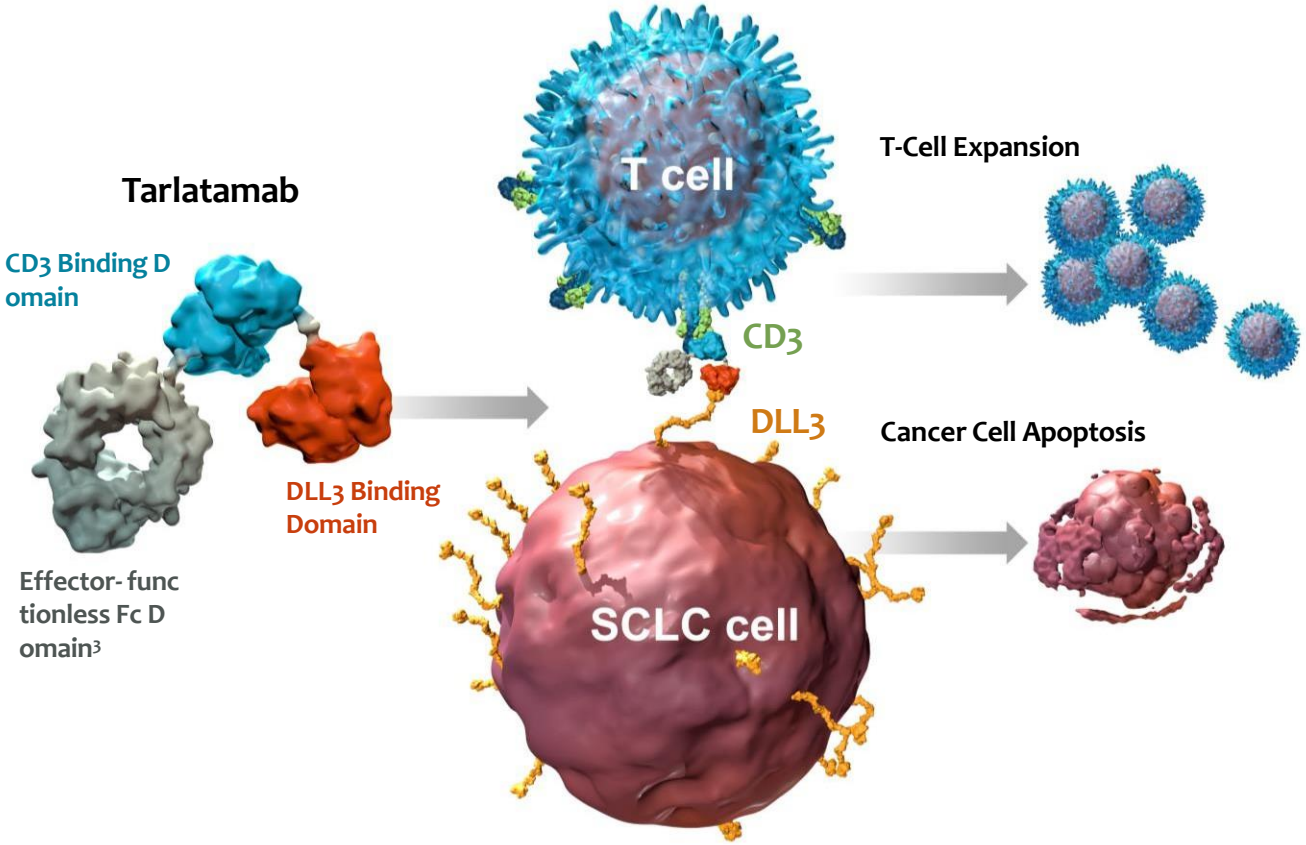


*Engineered to avoid simultaneous binding of CD3 and CD137.

Rudin. J Hematol Oncol. 2023;16(1):66. Su. Mol Cancer. 2024;23:97.

Tarlatamab is a BiTE® (Bispecific T-Cell Engager) Immunotherapy



Tarlatamab Mechanism of Action[1]

- Tarlatamab binds both DLL3 on cancer cells and CD3 on T cells, leading to T-cell mediated cancer cell lysis[1]
- Binding creates a cytolytic synapse between T cells and cancer cells, and can activate T cells without relying on MHC I[2,3]

CD3, cluster of differentiation 3; **DLL3**, Delta-like ligand 3; **Fc**, fragment crystallizable; **MHC I**, major histocompatibility complex class I; **SCLC**, small cell lung cancer.

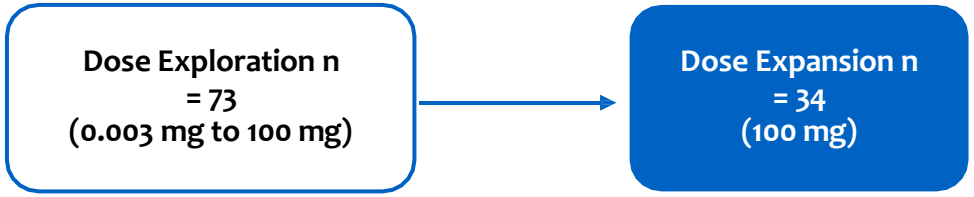
1. Owen DH, et al. *J Hematol Oncol*. 2019;12:61. 2. Nagorsen D, et al. *Exp. Cell Res.* 2011; 317:1255-1260. 3. Giffin MJ, et al. *Clin Cancer Res*. 2021;27:1526-1537.

DeLLphi-300

Phase 1 Dose Exploration/Expansion Study of Tarlatamab

Inclusion Criteria

- Histologically or cytologically confirmed SCLC
- Progressed or recurred following ≥ 1 platinum-based chemotherapy (including PD-L1 inhibitor if SOC)
- ≥ 2 measurable lesions
- ECOG performance status: 0–2
- If present, clinically/radiologically stable brain metastases following treatment



- Tarlatamab administered by IV infusion Q2W
- Step-dosing starting with the 3 mg cohort
  (1 mg run-in dose followed by target dose on day 8, day 15, and Q2W thereafter)

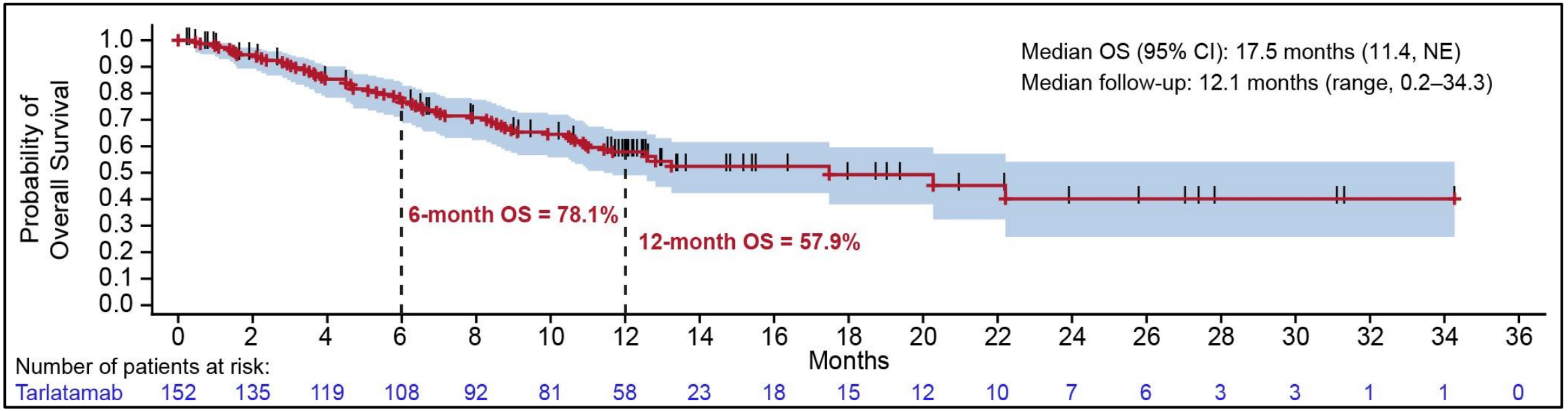
Primary	Safety, including DLTs, TE AEs, TRAEs
Secondary E ndpoints	▪ ORR*, DOR, TTR, PFS, OS, and PK

Data cut-off: July 19, 2022.
*per modified RECIST 1.1 by investigator assessment.
DLT, dose-limiting toxicity; **DOR**, duration of response; **ECOG**, Eastern Cooperative Oncology Group; **IV**, intravenous; **ORR**, objective response rate; **OS**, overall survival; **PD-L1**, programmed cell death ligand-1; **PFS**, progression-free survival; **PK**, pharmacokinetics; **Q2W**, every two weeks; **RECIST**, response evaluation criteria in solid tumors; **SCLC**, small cell lung cancer; **SOC**, standard-of-care; **TEAE**, treatment-emergent adverse events; **TRAE**, treatment-related adverse event; **TTR**, time to response.
Paz-Ares L, et al. *J Clin Oncol*. 2023;41:2893-2903.

DeLLphi-300

Phase 1 Dose Exploration/Expansion Study of Tarlatamab

Kaplan-Meier estimate of OS across clinically relevant (≥ 10 mg) dose levels*



Median follow-up: 12.1 months (range, 0.2–34.3)

- **Among 17 patients receiving the tarlatamab 10 mg dose, median OS was 20.3 months (95% CI: 5.1 to NE)**

*Vertical solid lines indicate censored data. Blue shading designates 95% confidence band.
NE, not estimable; **OS**, overall survival.
Hummel HD, et al. Presentation delivered at European Lung Cancer Congress 2024; March 20-23, 2024; Prague, CZE. Presentation 195MO.

DeLLphi-301

Phase 2, open-label study (NCT05060016)

Key Inclusion Criteria

- R/R SCLC
- Previous treatment with ≥ 2 lines (including platinum-doublet)
- ECOG PS 0–1
- Measurable disease
- Treated and stable brain me tastases allowed

R 1:1

Part 1: Dose Evaluation

Tarlatamab 10 mg IV infusion (n = 88)
1 mg on Day 1, followed by 10 mg on Days 8 and 15, and Q2W thereafter*,†

Tarlatamab 100 mg IV infusion (n = 88)
1 mg on Day 1, followed by 100 mg on Days 8 and 15, and Q2W thereafter*,†

ITT analysis set

Dose Selection‡

Part 2: Dose Expansion

Tarlatamab 10 mg (n = 12)
Same dosing as in Part 1

Part 3: Reduced Inpatient Monitoring Period

Tarlatamab 10 mg (n = 34)
Same dosing as in Part 1

Primary Efficacy Endpoint: ORR per RECIST 1.1 by BICR
Key Secondary Endpoints: DOR, DCR, PFS per RECIST 1.1 by BICR, OS, adverse events during the treatment period

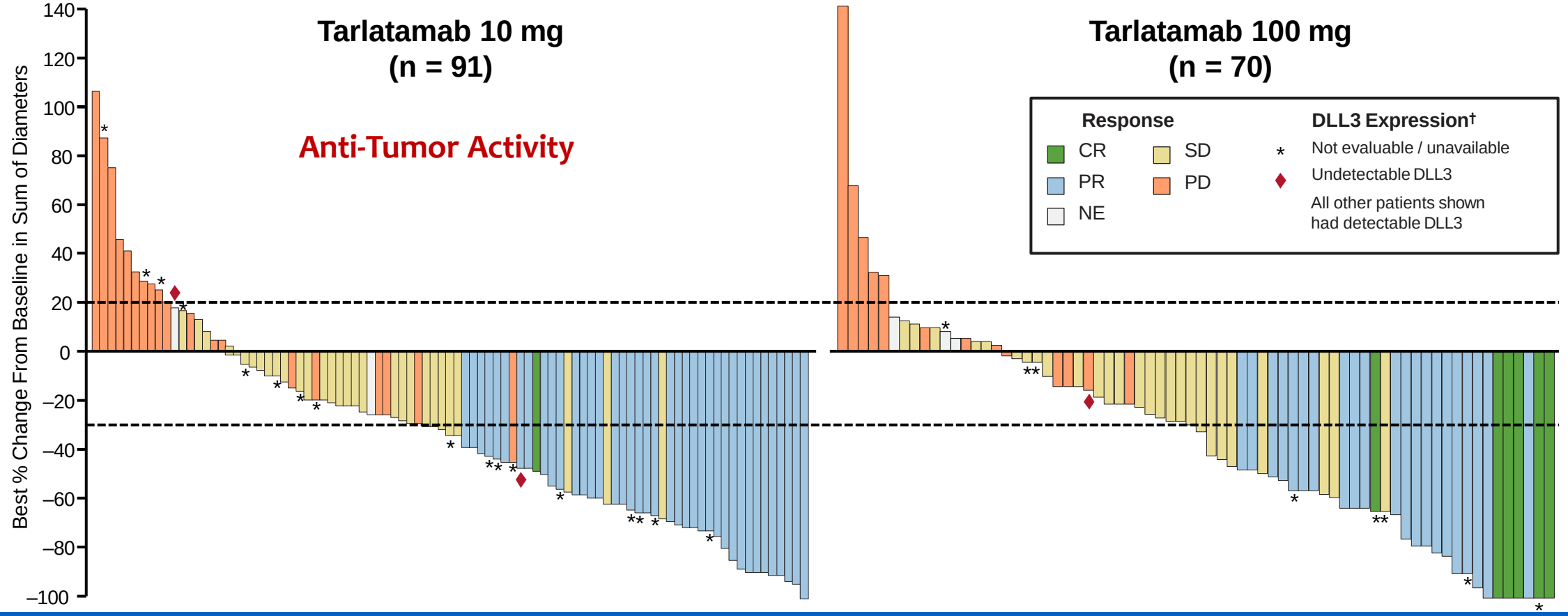
*Dexamethasone was administered on days 1 and 8 of cycle 1, and IV hydration was administered following all tarlatamab doses in cycle 1. †28-day cycles. ‡Once 30 patients per dose level had the opportunity to confirm an objective response after the first post-treatment scan or up to13 weeks of follow-up, 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; **IV**, intravenous; **ORR**, objective response rate; **OS**, overall survival; **PFS**, progression-free survival; **Q2W**, every 2 weeks; **R**, randomization; **R/R**, relapse/refractory; **RECIST**, Response Evaluation Criteria in Solid Tumors; **SCLC**, small cell lung cancer.
1. Ahn MJ, et al. *N Engl J Med*. 2023;389:2063-2075. 2. Ahn MJ, et al. *N Engl J Med*. 2023;389:2063-2075; Appendix.

DeLLphi-301

Baseline Characteristics	Parts 1 + 2 Tarlatamab 10 mg (n = 100)	Part 1 Tarlatamab 100 mg (n = 88)	Part 3 Tarlatamab 10 mg (n = 34)
Median age, years (range)	64 (35–82)	62 (34–80)	66 (49–80)
Male, %	72	70	71
Asian / Black or African American / White,* %	41 / 0 / 58	41 / 0 / 58	6 / 3 / 91
Ever smoker / non-smoker, %	92 / 8	94 / 6	97 / 3
ECOG performance status: 0 / 1, %	26 / 74	27 / 73	29 / 71
Prior lines of therapy, median (range)	2 (1–6)	2 (1–8)	2 (2–6)
2 prior lines of therapy, %	65	55	65
≥ 3 prior lines of therapy, %	33	43	35
Prior anti-PD-(L)1 treatment, %	73	70	82
< 90 days to progression after first-line platinum therapy,† %	28	20	21
Brain / liver metastases, %	23 / 39	36 / 34	12 / 35
DLL3 expression (> 0%), n/N evaluable (%)	80/83 (96)	71/74 (96)	N/A

Data cutoff, June 27, 2023. Median follow-up was 10.6 months for tarlatamab 10 mg and 10.3 months for tarlatamab 100 mg.
*No patients of American Indian, Alaska Native, Native Hawaiian, or other Pacific Islander race were enrolled. †Platinum sensitivity was calculated as the interval between the end of first-line platinum therapy to date of first progression.
DLL3, delta-like ligand 3; **ECOG**, Eastern Cooperative Oncology Group; **N/A**, not applicable; **PD-(L)1**, programmed cell death protein-1/programmed cell death ligand-1.
Ahn MJ, et al. *N Engl J Med*. 2023;389:2063-2075.

DeLLphi-301



Responses were observed regardless of DLL3 expression, as well as in patients without evaluable tumor tissue

Shown are 91 of 100 patients (tarlatamab 10 mg) and 70 of 88 patients (tarlatamab 100 mg) who had available post-baseline measurements of target lesions.
†DLL3 expression was assessed by immunohistochemistry of tumor tissue samples.
CR, complete response; **DLL3**, delta-like ligand 3; **NE**, not evaluable; **PD**, progressive disease, **PR**, partial response; **SD**, stable disease.
Ahn MJ, et al. *N Engl J Med*. 2023;389:2063-2075; Appendix.

DeLLphi-301

Tarlatamab 10 mg demonstrated anti-tumor activity in heavily pre-treated SCLC with an objective response rate of 40%

Outcome	Tarlatamab 10 mg (n = 100)	Tarlatamab 100 mg (n = 88)
Objective response rate, n (%) (97.5% CI)	40 (40) (29, 52)	28 (32) (21, 44)
Complete response, n (%)	1 (1)	7 (8)
Partial response, n (%)	39 (39)	21 (24)
Stable disease, n (%)	30 (30)	27 (31)
Progressive disease, n (%)	20 (20)	13 (15)
Not evaluable, n (%)†	2 (2)	4 (5)
Death before post-baseline scan, n (%)†	6 (6)	13 (15)
No post-baseline scan, n (%)†	2 (2)	3 (3)
Observed duration of response ≥ 6 months, n/N (%)	23/40 (58)	17/28 (61)
Disease control rate, n (%) (95% CI)	70 (70) (60, 79)	55 (63) (52, 73)

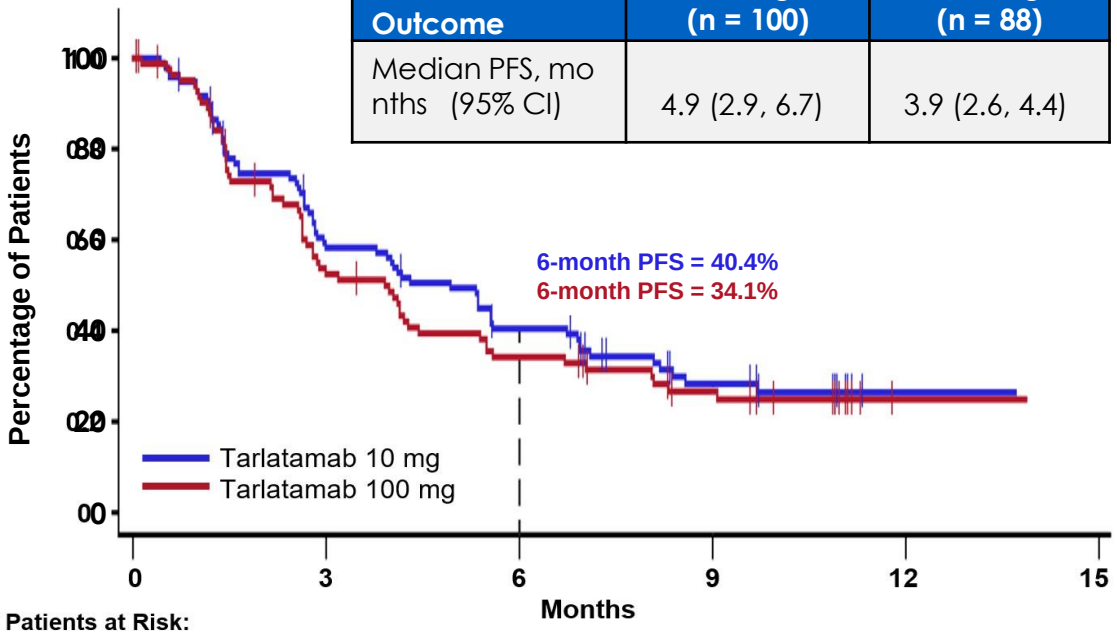
*Data cutoff, June 27, 2023. Median follow-up was 10.6 months for tarlatamab 10 mg and 10.3 months for tarlatamab 100 mg. The efficacy analysis set consists of patients in Parts 1 and 2 (N = 188). Part 3 did not have adequate follow-up for response analysis. †In the response analysis, patients who could not be evaluated, who died before the postbaseline scan, or who did not have a postbaseline scan were considered not to have had an objective response. **SCLC**, small cell lung cancer.

Ahn MJ, et al. *N Engl J Med*. 2023;389:2063-2075.

DeLLphi-301 PFS and OS

OS data is not yet mature; at the last follow-up 57% of patients in the tarlatamab 10 mg group and 51% of patients in the tarlatamab 100 mg group were still alive

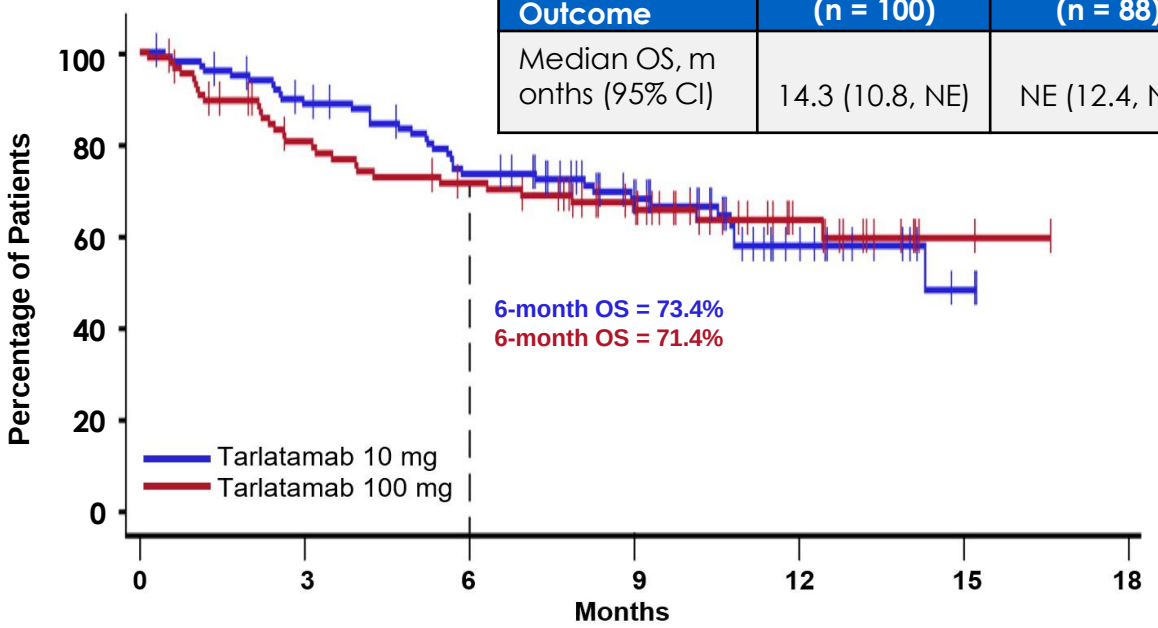
Outcome	Tarlatamab 10 mg (n = 100)	Tarlatamab 100 mg (n = 88)
Median PFS, months (95% CI)	4.9 (2.9, 6.7)	3.9 (2.6, 4.4)



Number of Patients at Risk:

Tarlatamab 10 mg	100	53	35	18	2	0
Tarlatamab 100 mg	88	41	26	15	3	0

Outcome	Tarlatamab 10 mg (n = 100)	Tarlatamab 100 mg (n = 88)
Median OS, months (95% CI)	14.3 (10.8, NE)	NE (12.4, NE)



Tarlatamab 10 mg	100	84	67	44	17	3	0
Tarlatamab 100 mg	88	62	53	39	16	2	0

Median follow-up was 10.6 months for tarlatamab 10 mg and 10.3 months for tarlatamab 100 mg.
CI, confidence interval; **NE**, not evaluable; **OS**, overall survival; **PFS**, progression-free survival.

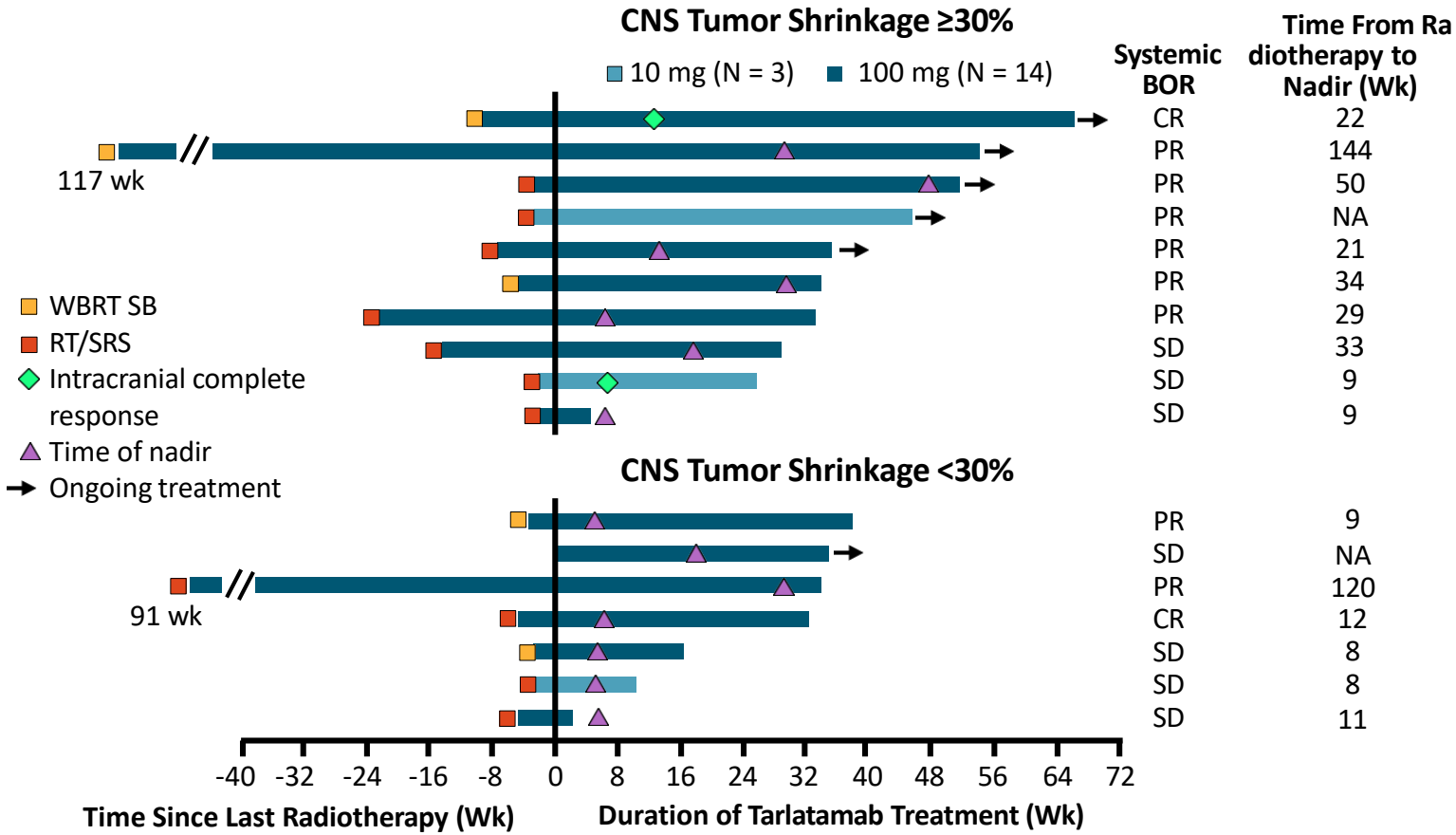
1. Ahn MJ, et al. *N Engl J Med*. 2023;389:2063-2075.

DeLLphi-301 (Intracranial Anti-tumor Activity)

Tarlatamab 10 mg (n = 3) or 100 mg (n = 14) Q2W with baseline CNS lesions ≥10 mm

mRANO-BM analyses (N = 17)

- 10/17 (30%) had CNS tumor shrinkage
- 16/17 (94%) had intracranial disease control (95% CI: 71.3-99.9)
- Median duration of intracranial dise ase control was NE (2.6-13.9+ mo)
- 3/17 (18%) had CNS disease progre ssion per mRANO-BM



Dingemans. ASCO 2024. Abstr 8015.

Summary of Adverse Events

TEAEs[1], n (%)	Parts 1 + 2 Tarlatamab 10 mg (n = 99)	Part 1 Tarlatamab 100 mg (n = 87)	Part 3 Tarlatamab 10 mg (n = 34)
Any grade	96 (97)	87 (100)	34 (100)
≥ Grade 3	57 (58)	56 (64)	22 (65)
Related to tarlatamab, any grade	89 (90)	81 (93)	29 (85)
≥ Grade 3	29 (29)	29 (33)	5 (15)
Fatal	0	0	1 (3)†
Leading to dose interruption/reduction	14 (14)	25 (29)	3 (9)
Leading to discontinuation	4 (4)	3 (3)	0

Most Common TEAEs in ≥ 20% of Patients[2], n (%)	Parts 1 + 2 Tarlatamab 10 mg (n = 99)	Part 1 Tarlatamab 100 mg (n = 87)	Part 3 Tarlatamab 10 mg (n = 34)
CRS	49 (49)	53 (61)	19 (56)
Decreased appetite	25 (25)	38 (44)	13 (38)
Pyrexia	38 (38)	29 (33)	8 (24)
Constipation	28 (28)	22 (25)	8 (24)
Anemia	26 (26)	22 (25)	9 (26)
Asthenia	20 (20)	21 (24)	10 (29)
Dysgeusia	24 (24)	12 (14)	14 (41)
Fatigue	21 (21)	17 (20)	9 (26)

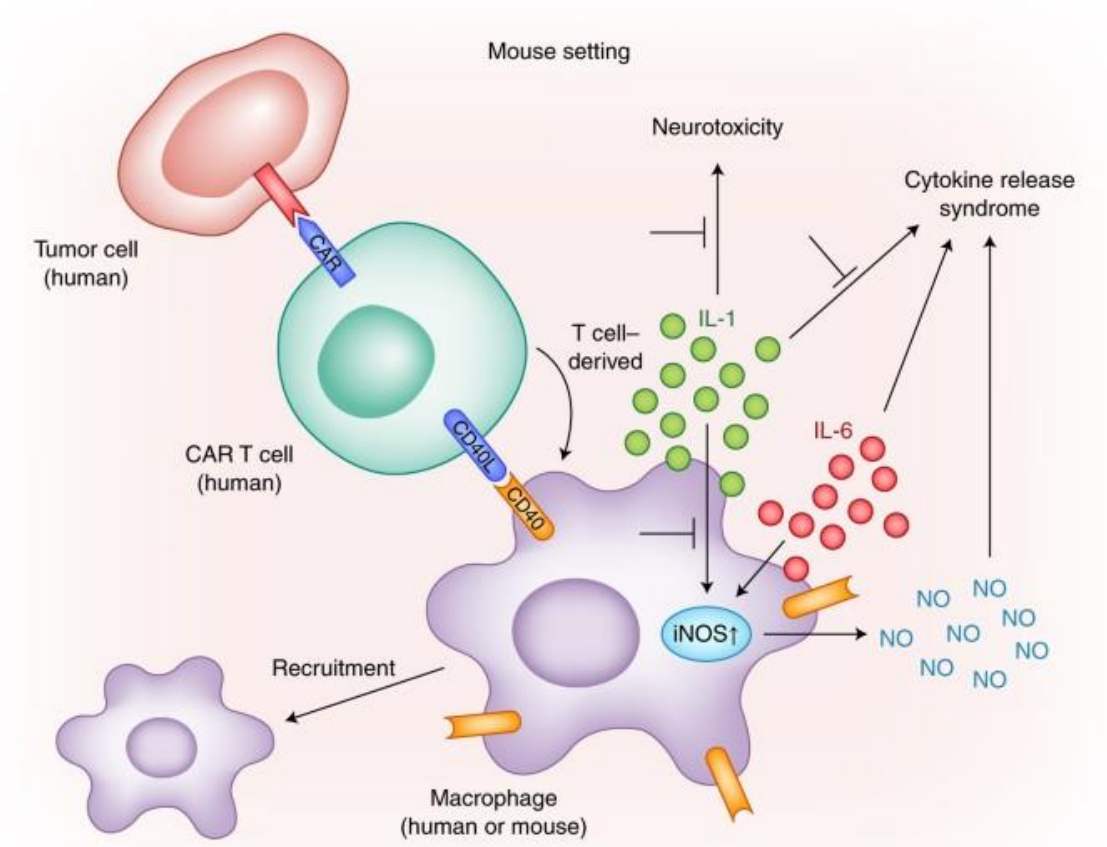
- **Tarlatamab demonstrated a manageable safety profile, with a low rate of discontinuations due to TRAEs**

*The safety analysis set includes all patients in Part 1, Part 2, and Part 3 who received at least one dose of tarlatamab (N = 220)[1]. †Fatal TRAE was respiratory failure.[1] The patient had a grade 5 respiratory failure with potentially contributing factors including baseline chronic obstructive pulmonary disease requiring supplemental oxygen, baseline compromised functional reserve, concurrent grade 3 cytokine release syndrome and pneumonitis after C1D1 treatment, and a decision against escalation to ICU-level care.[2] **CRS**, cytokine release syndrome; **TEAE**, treatment-emergent adverse event; **TRAE**, treatment- related adverse event.

1. Ahn MJ, et al. *N Engl J Med*. 2023;389:2063-2075. 2. Ahn MJ, et al. *N Engl J Med*. 2023;389:2063-2075; Appendix.

DeLLphi-301 : Tarlatamab Toxicities—CRS and ICANS

- **Common symptoms[1]**
  - Fever, hypotension, and hypoxia
- **Timing and resolution[1]**
  - Median onset following last tarlatamab dose: 13 hours (IQR: 8–27)
  - Median duration: 4 days (range, 2–6)
  - Resolution in 98% of cases
- **CRS Recurrence[2]**
  - 24% of patients had another CRS event (pri marily Grade 1) with a subsequent dose[2]
- **Dose interruption, dose reduction, or both[1]**
  - 10 mg group: 4 patients (3%)
  - 100 mg group: 8 patients (9%)

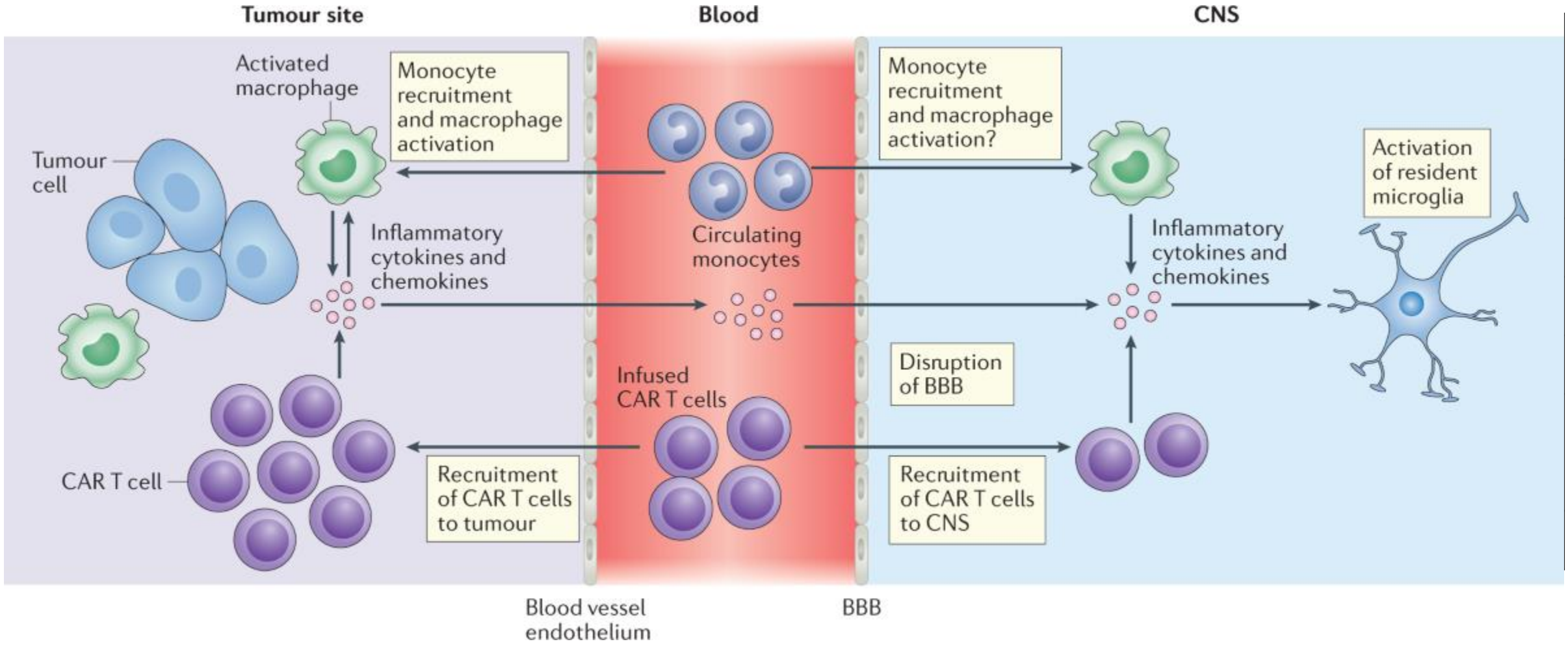


CRS was predominately grade 1 or 2 in severity

CRS, cytokine release syndrome; **IQR**, interquartile range.

1. Ahn MJ, et al. *N Engl J Med*. 2023;389:2063-2075. 2. Gray S, et al. Oral presented at the Oncology Nursing Society (ONS) Congress: April 24-28, 2024; Washington, DC. Poster Monitor 24.

DeLLphi-301 : Tarlatamab Toxicities—CRS and ICANS



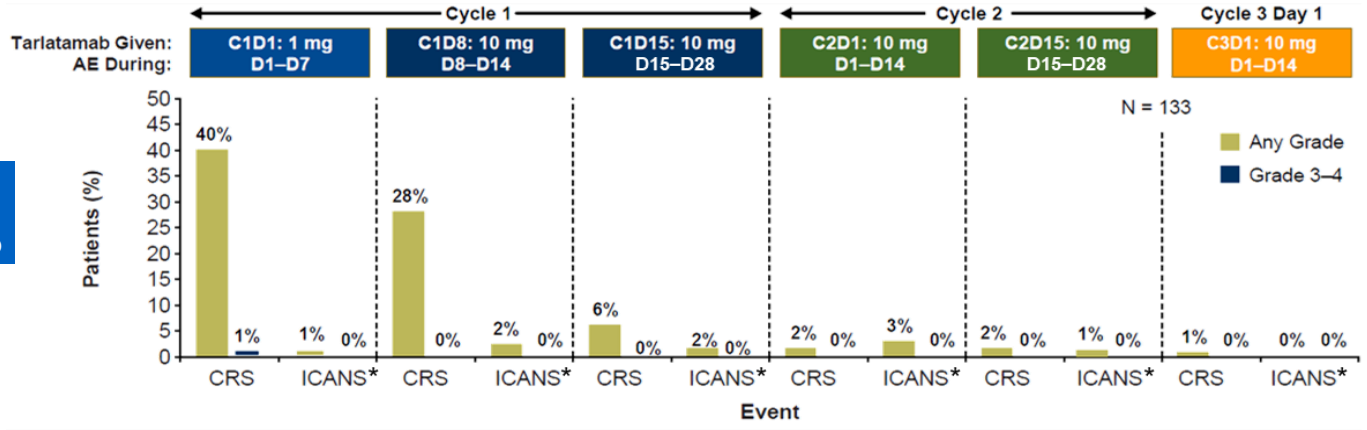
*ICANS includes associated neurologic events based on a broad search using 61 selected preferred terms from MedDRA version 26.0.
AE, adverse event; **CI**, confidence interval; **ICANS**, immune effector cell-associated neurotoxicity syndrome; **MedDRA**, Medical Dictionary for Regulatory Activities. A hn MJ, et al. *N Engl J Med*. 2023;389:2063-2075.

DeLLphi-301 : Tarlatamab Toxicities—CRS and ICANS

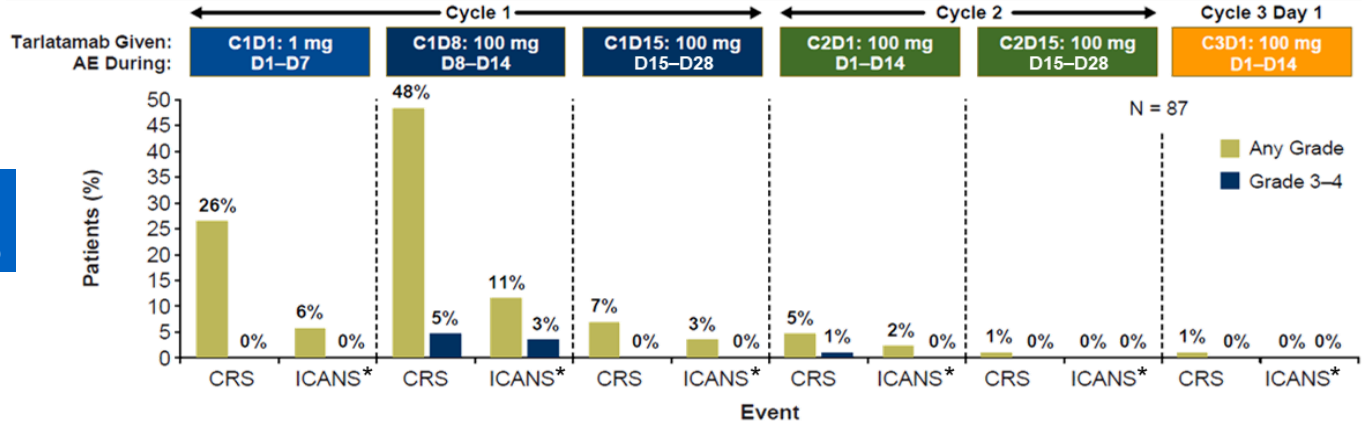
CRS : Cytokine Release Syndrome

ICANS : Immune Effector Cell- Associated Neurotoxicity Syndrome

10 mg Tarlatamab



100 mg Tarlatamab



- **CRS :** Earlier compared to CAR T-induced CRS, within a **few hours** of administration; **largely confined to the first or second dose**
- **ICANS* : infrequently overall and was predominantly observed with tarlatamab 100mg**

*ICANS includes associated neurologic events based on a broad search using 61 selected preferred terms from MedDRA version 26.0.
AE, adverse event; **C**, cycle; **CRS**, cytokine release syndrome; **D**, day; **ICANS**, immune effector cell-associated neurotoxicity syndrome; **MedDRA**, medical dictionary for regulatory activities.
Ahn MJ, et al. *N Engl J Med*. 2023;389:2063-2075.

DeLLphi-301 : Conclusion

- **Tarlatamab 10 mg** demonstrated durable anticancer activity, promising survival outcomes, and a manageable safety profile
  - **ORR** was **40%**, observed DOR was ≥ 6 months in 59% of responders, 6-month PFS was 40%, and 6-month OS was 73%
  - The most common TEAE was CRS, which primarily occurred in cycle 1, was mostly grade 1–2, and was generally manageable with supportive care
  - **Discontinuation** of tarlatamab due to TRAEs was **low (3%)**
  - Shorter inpatient monitoring (Part 3) did not alter the safety profile

- Tarlatamab 10 mg was the selected dose for further clinical development
- Longer follow-up of patients in this trial will provide better clarity on the long-term response durability and survival benefits
- The ongoing phase 3 **DeLLphi-304 study** will compare the efficacy and safety of tarlatamab (10 mg Q2W) with standard-of-care chemotherapy

Tarlatamab Clinical Development Program in SCLC

Trial	Phase	Line of therapy, treatment
DeLLphi-300, NCT03319940[1]	Phase 1	2L+, monotherapy and with anti-PD-1
DeLLphi-301, NCT05060016[2]	Phase 2	3L+, monotherapy
DeLLphi-302, NCT04885998[3]	Phase 1b	2L+, with anti-PD-1
DeLLphi-303, NCT05361395[4]	Phase 1b	1L in ES-SCLC, with carboplatin, etoposide, and PD-L1 inhibitor
DeLLphi-304, NCT05740566[5]	Phase 3	2L, monotherapy vs SOC chemotherapy
DeLLphi-305, NCT06211036[6]	Phase 3	1L maintenance in ES-SCLC after immunochemotherapy, tarlatamab and durvalumab vs durvalumab alone
DeLLphi-306, NCT06117774[7]	Phase 3	1L after chemoradiotherapy in LS-SCLC, monotherapy vs placebo

1L, first-line; **2L**, second-line; **3L**, third-line; **ES**, extensive-stage; **LS**, limited-stage; **PD-1**, programmed cell death protein-1; **PD-L1**, programmed cell death ligand-1; **SCLC**, small cell lung cancer; **SOC**, standard of care.

1. ClinicalTrials.gov. Accessed August 1, 2024. https://clinicaltrials.gov/ct2/show/NCT03319940 2. ClinicalTrials.gov. Accessed August 1, 2024. https://clinicaltrials.gov/ct2/show/NCT05060016 3. ClinicalTrials.gov. Accessed August 1, 2024. https://clinicaltrials.gov/ct2/show/NCT04885998 4. ClinicalTrials.gov. Accessed August 1, 2024. https://clinicaltrials.gov/ct2/show/NCT05361395 5. ClinicalTrials.gov. Accessed August 1, 2024. https://clinicaltrials.gov/ct2/show/NCT05740566 6. ClinicalTrials.gov. Accessed August 1, 2024. https://clinicaltrials.gov/study/NCT06211036 7. ClinicalTrials.gov. Accessed August 1, 2024. https://clinicaltrials.gov/study/NCT06117774

Tarlatamab

CLINIGENDIRECT

[Importance Notice] New Applications for S. Korea Tarlatamab Expanded Access Program (EAP) will be closed on April 1st, 2025

Dear Healthcare Professional,

Thank you for your interest and participation in the Tarlatamab Expanded Access Program (EAP).

Due to a higher-than-anticipated number of applications and a limited drug supply, we regret to inform you that further new application for the Tarlatamab EAP will be discontinued to ensure continued treatment for patients who have already enrolled.

Effective April 1, 2025, the program will stop accepting new patient applications. Any applications that are not fully completed, submitted, and deemed eligible by this date will not be eligible to be included in the EAP.

For patients currently receiving therapy, please continue submitting refill

💰 환자의 예상 치료 비용 (170cm, 60kg 기준)

✅ **초기 투여 비용 (1주 차)**

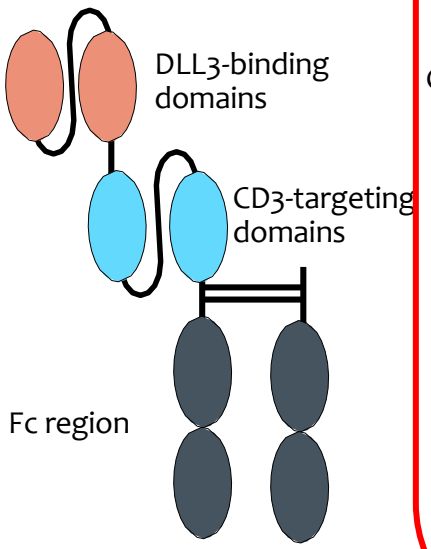
- 1mg: **약 4,186,500원**
- 10mg: **약 37,696,500원**
  ➡️ **총 41,883,000원**

✅ **유지 투여 비용 (매 2주마다 10mg 투여)**

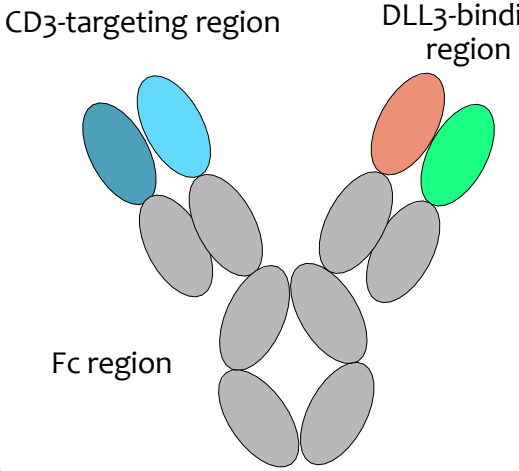
- 10mg = **약 37,696,500원**
- **6개월 치료 (12회 투여): 약 4억 5천 6백만 원**
- **1년 치료 (24회 투여): 약 9억 원**

DLL3 T-Cell Engagers in Development

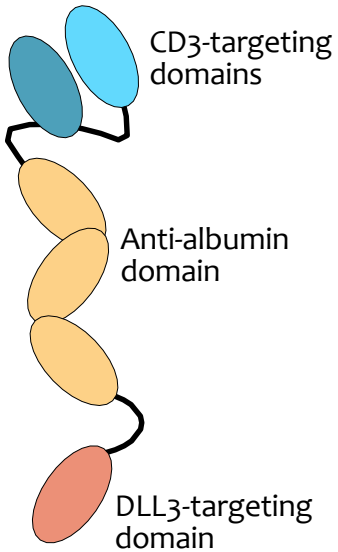
Tarlatamab



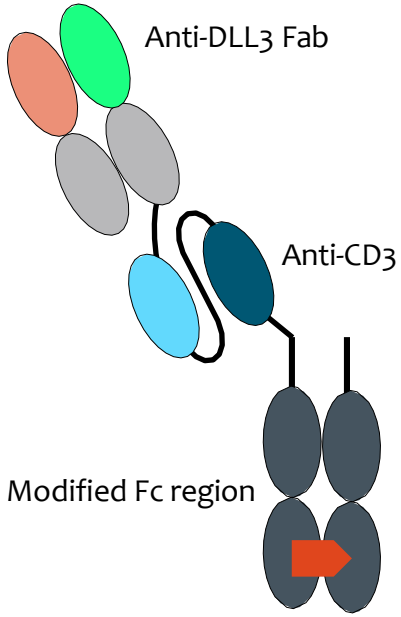
BI 764532



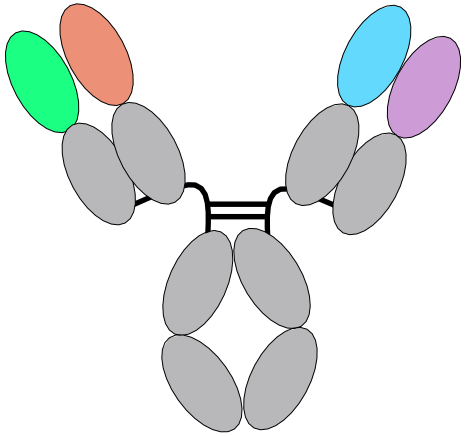
MK-6070 (HPN 328)



QLS31904



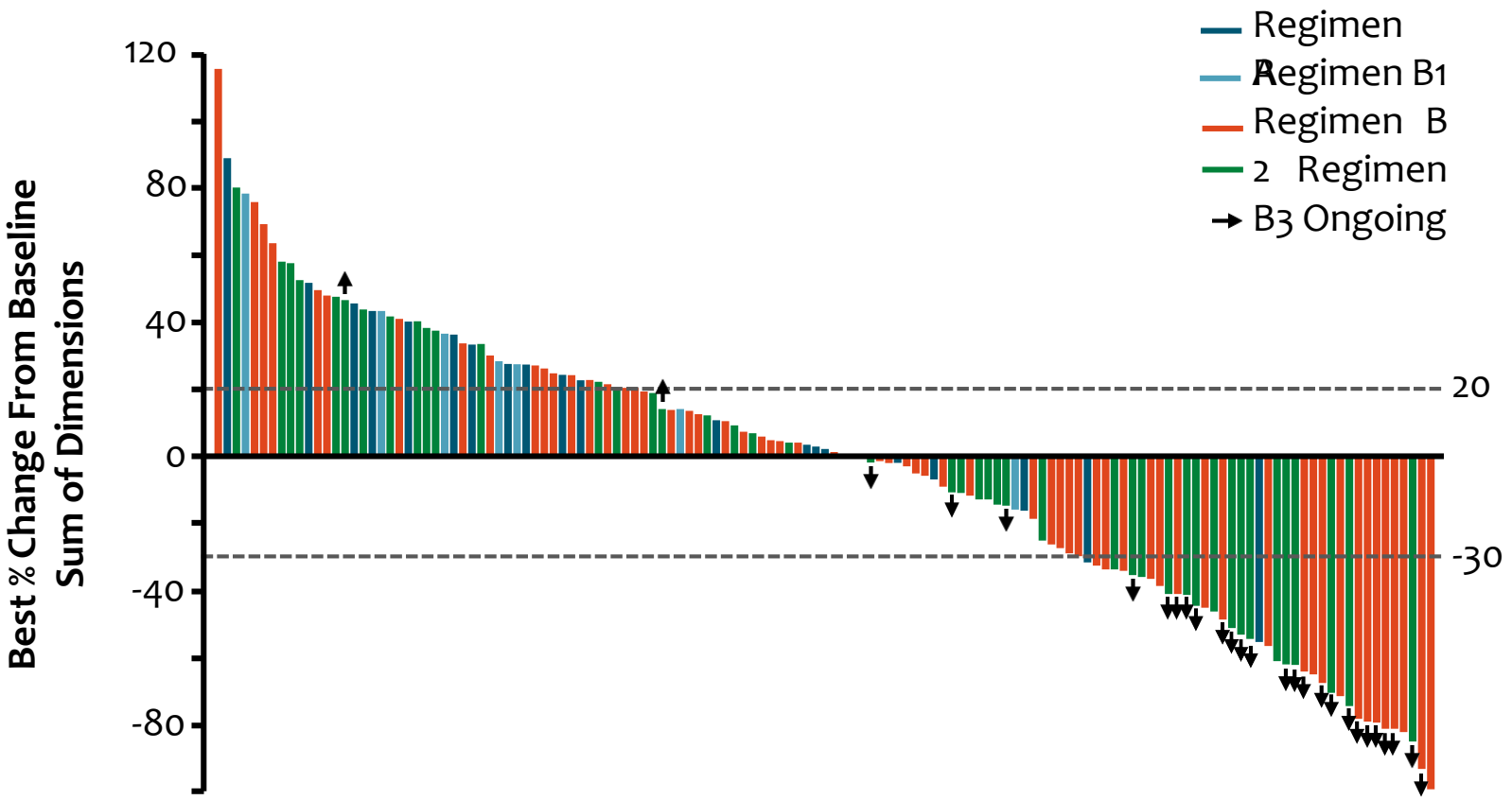
RO7616789



*Engineered to avoid simultaneous binding of CD3 and CD137.

Rudin. J Hematol Oncol. 2023;16(1):66. Su. Mol Cancer. 2024;23:97.

Phase I Study of Obrixtamig(BI 764532) Response Summary



Response, n (%)	Obrixtamig All (N = 154)*
ORR	27 (18)
PR	27 (18)
SD	37 (24)
PD	60 (39)
DCR	64 (42)

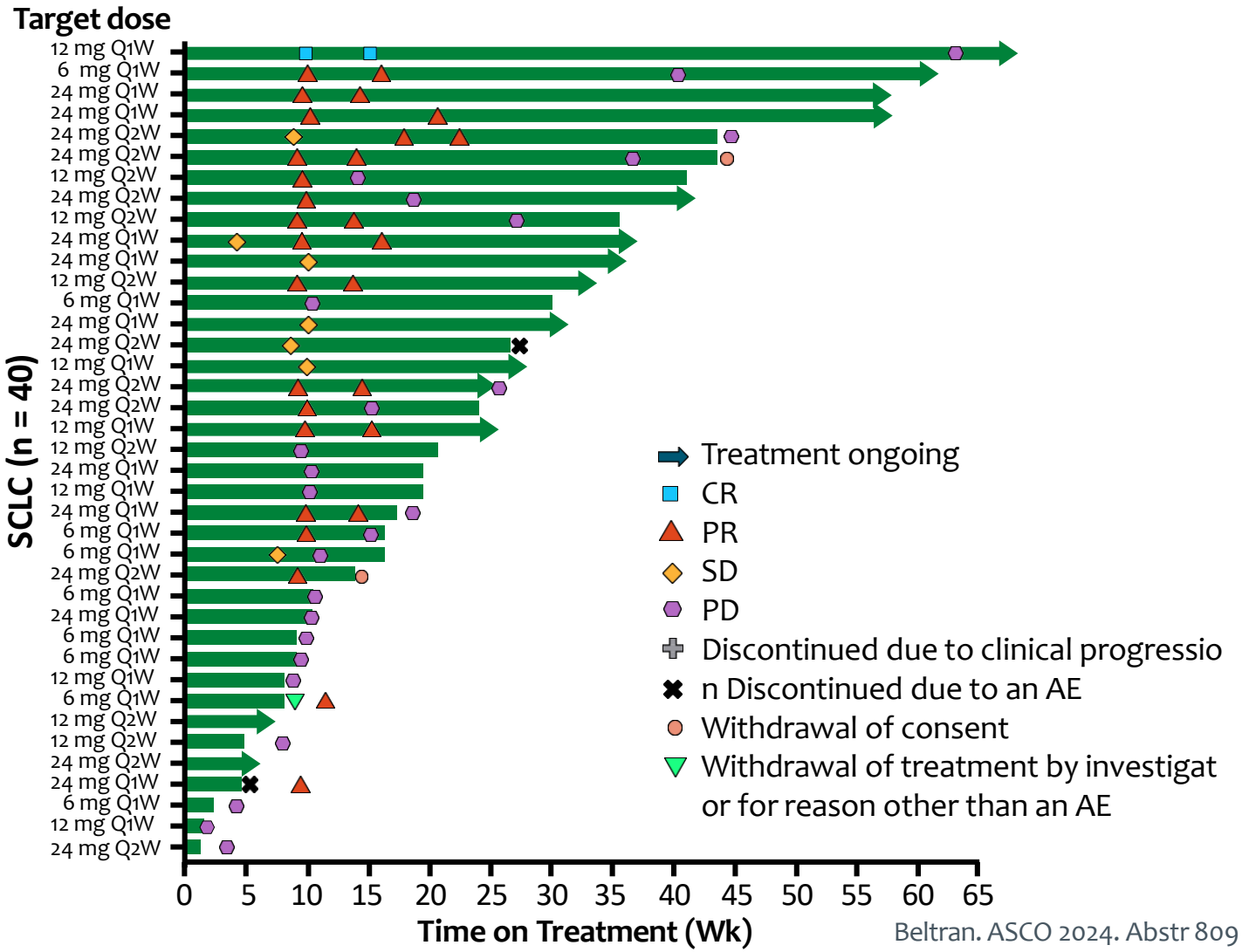
*Efficacy population: ≥1 postbaseline tumor assessment or permanently discontinued prior to tumor assessment; responses evaluated per RECIST v1.1.

Wermke. ESMO 2024. Abstr 670P.

Phase I/II Trial of MK-6070: Efficacy/Safety Summary

Response, n (%)	SCLC (n = 28)	Other NEN (n = 13)
Overall		
▪ ORR	11 (39)	6 (46)
▪ DCR	20 (71)	6 (46)
Extracranial		
▪ ORR	14 (50)	6 (46)
▪ DCR	21 (75)	6 (46)

Treatment-Related AEs (Incidence ≥20%)	Any Grade	Grade ≥3
CRS (%)	**61 (63)**	**3 (3)**
Fatigue (%)	36 (37)	2 (2)
Dysgeusia (%)	35 (36)	0
Nausea (%)	22 (23)	0
Vomiting (%)	20 (21)	0

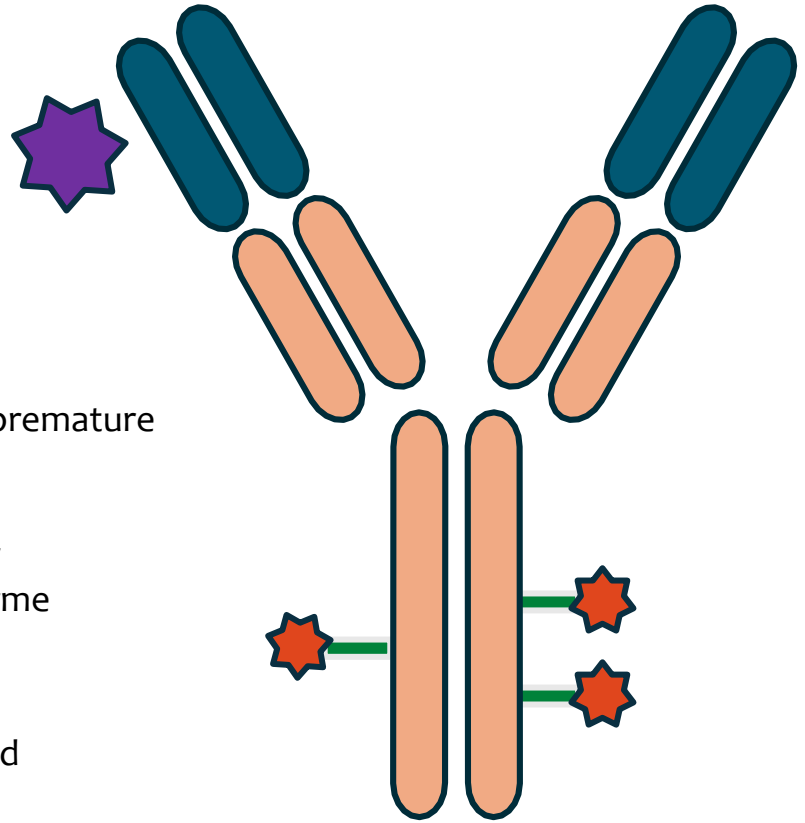


Beltran. ASCO 2024. Abstr 809

07 ADCs(antibody drug conjugates) : Key structural elements

Target

- Tumor specific with homogeneous and high levels of expression
- No to minimal expression on normal tissue



Antibody

- Homogenous expression on tumor cells may enhance treatment response
- IgG1 is the most used mAb
  - IgG1 is effective in activating immune responses such as ADCC and CDCC

Linker

Stability: Must be stable in plasma to prevent premature release of the payload

Cleavable linker

- Release payload within the target cell under specific conditions. Ex acidic or specific enzyme
- Enhanced bystander effect

Non-Cleavable linker

- Remain intact and do not release the payload until entire ADC is degraded
- Limits diffusion to nearby cells and bystander effect

Payload

Cytotoxic mechanism

- Topoisomerase-I inhibitor
- Microtubule inhibitors

Potency

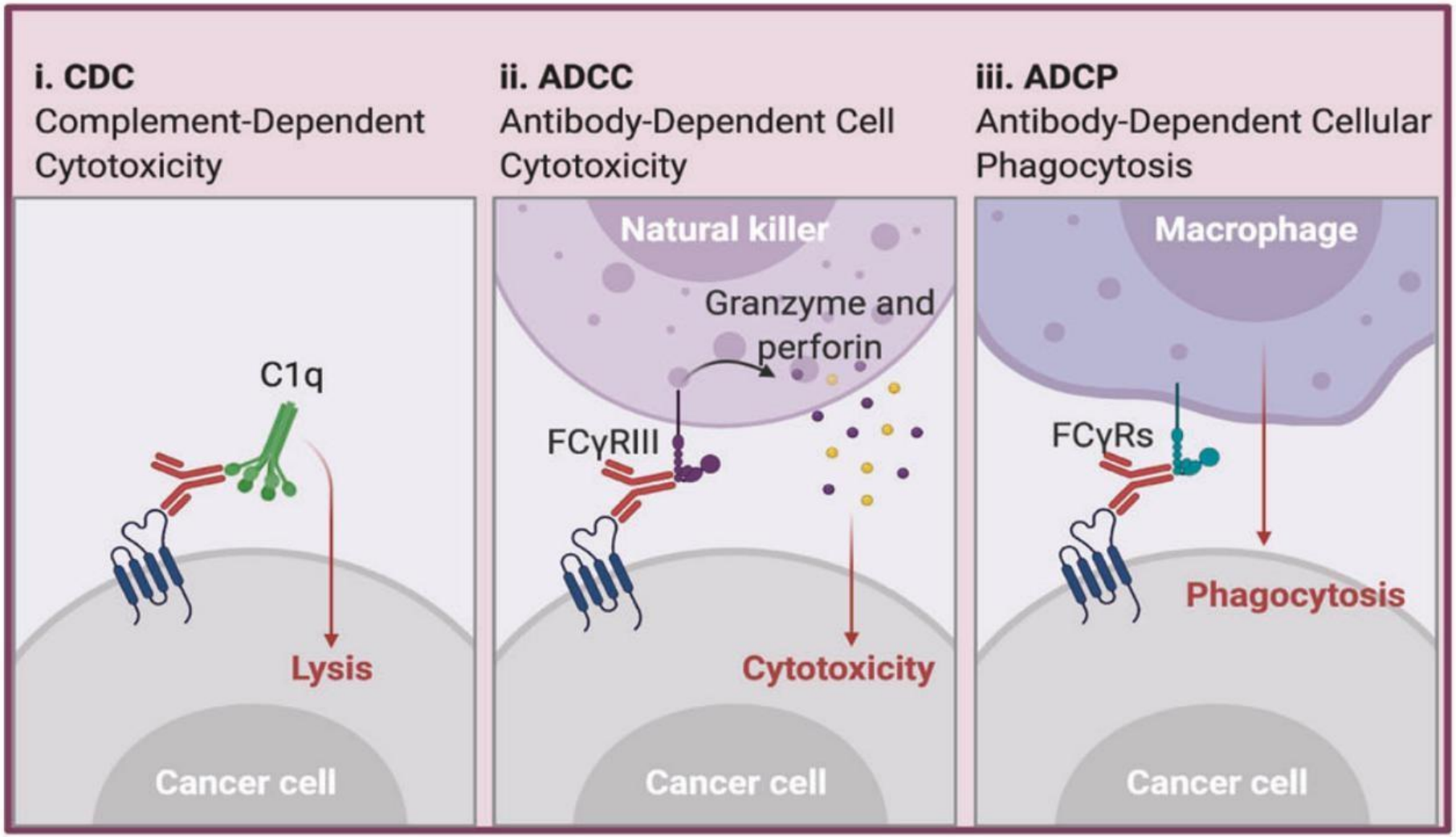
- ADC payloads (subnanomolar IC50) are ~100-1000x more potent than small-molecule chemotherapeutic payloads

Antibody-drug ratio (ADR)

- Usually 4-8

Theocharopoulos. Vaccines (Basel). 2021;9:1111.

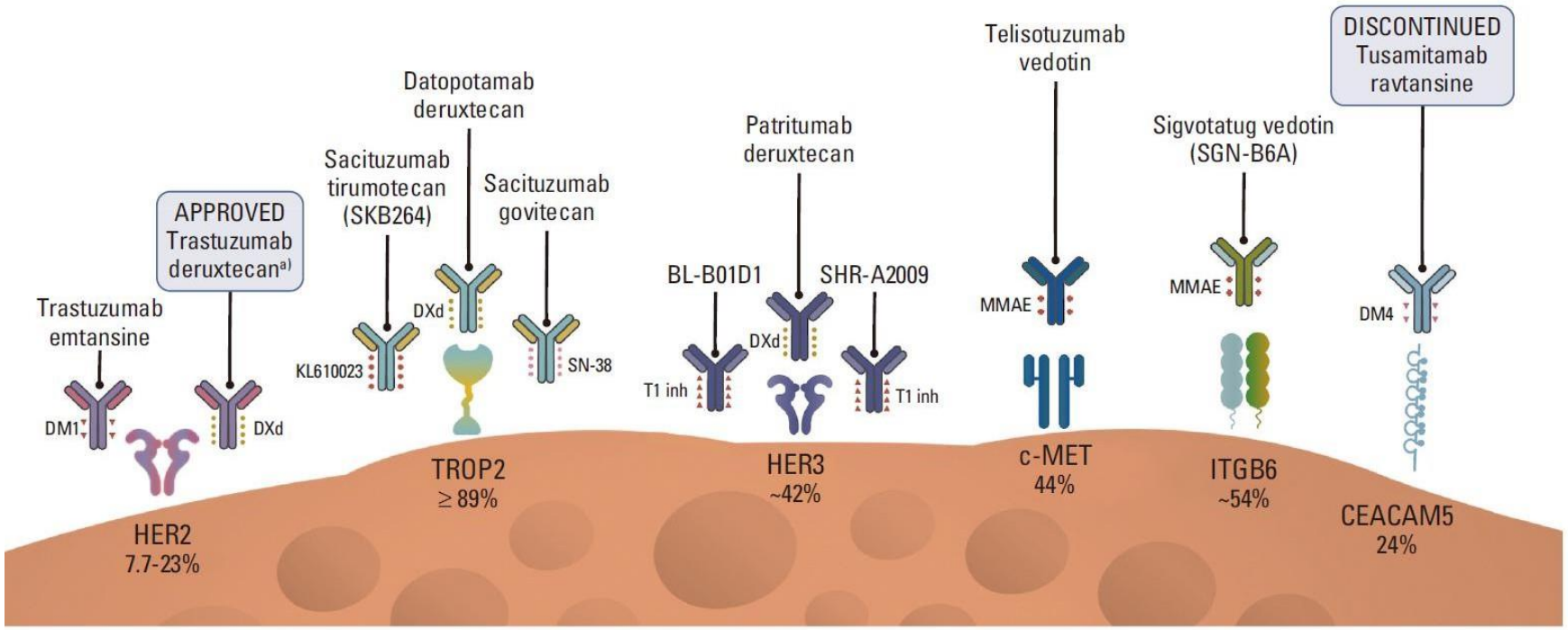
ADCs: Mechanism

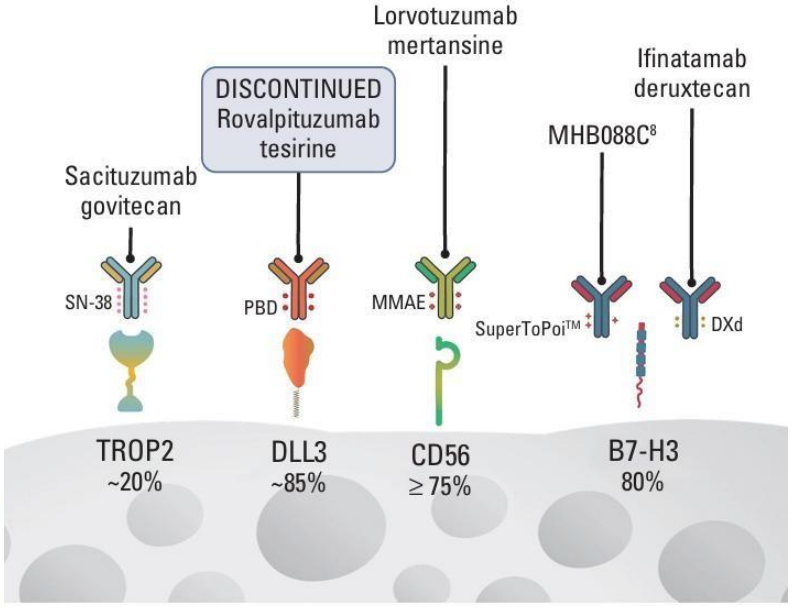


Fu, Z.et al. Sig Transduct Target Ther 7, 93 (2022).

ADCs elicit antitumor immunity including CDC, ADCC and ADCP effect

Targets & ADCs in Lung cancer





M Riudavets et al. Cancer Res Treat. 2024 Nov 28. Online ahead of print.

Promising ADCs in Clinical Development for SCLC

Target	Prevalence, %	Agent	Payload	Early Phase Results	Toxicities
B7-H3[1-3]	65	DS-7300 (I-DXd)	Deruxtecan	**Phase II (n = 42, 12 mg/kg)** ORR: 52.4% **Phase I/II (n = 21); ORR: 52.4%** mDoR: 5.9 mo mPFS: 5.6 mo mOS: 12.2 mo	Fatigue, anemia, neutropenia, ILD

690P **Ifinatamab deruxtecan (I-DXd; DS-7300) in patients with advanced solid tumors: Updated clinical and biomarker results from a phase I/II study**

M.R. Patel[1], T. Doi[2], T. Koyama[3], G.S. Falchook[4], C.F. Friedman[5], S.A. Piha-Paul[6], M. Gutierrez[7], M.M. Awad[8], A.H. Mattour[9], T. Satoh[10], N. Okamoto[11], J. Singh[12], N. Yoshizuka[13], M. Qian[14], X. Qian[15], B.P. Tran[16], O. Dosunmu[17], P. Lu[18], M.L. Johnson[18]

Table: 690P Efficacy

	CRPC	ESCC	sqNSCLC	SCLC
No. of prior lines, median (range)	6 (1 – 11)	4 (1 – 7)	3 (1 – 12)	2 (1 – 9)
ORR by RECIST v1.1 (confirmed)	n = 59	n = 28	n = 13	n = 21
n (%)	15 (25)	6 (21)	4 (31)	11 (52)
DOR by RECIST v1.1	n = 59	n = 28	n = 13	n = 21
Median, mo (95% CI)	6.4 (2.8 – 10.6)	3.5 (2.4 – NE)	4.1 (2.8 – NE)	5.9 (2.8 – 7.5)
PFS by RECIST v1.1	n = 73	n = 28	NR	n = 21
Median, mo (95% CI)	4.8 (3.9 – 5.9)	2.8 (1.6 – 4.2)		5.8 (3.9 – 8.1)
OS	n = 73	n = 28	NR	n = 21
Median, mo (95% CI)	13.5 (10.3 – 16.6)	7.0 (4.8 – 12.2)		9.9 (5.8 – NE)

DOR, duration of response; NE, not estimable; NR, not reported; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors.

1. Carvajal-Hausdorf. J Immunother Cancer. 2019;7:65. 2. Rudin. WCLC 2024. Abstr OA04.03. 3. Johnson. WCLC 2023. Abstr 3258.
4. Wang. WCLC. 2024. Abstr OA04.06. 5. Wang. WCLC 2024. Abstr P3.13D.09. 6. Morgensztern. Clin Cancer Res. 2024;30:5042.
7. Chandana. ASCO 2024. Abstr 301. SEZ6 : Seizure-related homologue protein 6

Contents

Summary

Limited disease

Concurrent CTx(Etoposide + platinum) + RTx followed by PCI

Consolidation Tx ; Durvalumab

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NCCN Guidelines Version 4.2025
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PRINCIPLES OF SYSTEMIC THERAPY

PRIMARY OR ADJUVANT THERAPY FOR LIMITED STAGE SCLC:

Four cycles of cytotoxic chemotherapy are recommended.
Planned cycle length should be every 21–28 days during concurrent RT.
During cytotoxic chemotherapy + RT, cisplatin/etoposide is recommended (category 1).
The use of myeloid growth factors is not recommended during concurrent cytotoxic chemotherapy therapy plus RT (category 1 for not using GM-CSF).[1]

Preferred Regimens
- **Cisplatin 75 mg/m² day 1 and etoposide 100 mg/m² days 1, 2, 3[2]**
- **Cisplatin 60 mg/m² day 1 and etoposide 120 mg/m² days 1, 2, 3[3]**
- **Consolidation Therapy**
  - **Durvalumab 1500 mg day 1 every 28 days (category 1)[a,4]**

Other Recommended Regimens
- **Cisplatin 25 mg/m² days 1, 2, 3 and etoposide 100 mg/m² days 1, 2, 3[2]**
- **Carboplatin area under the curve (AUC) 5–6 day 1 and etoposide 100 mg/m² days 1, 2, 3[b,5]**

Summary

Extensive disease

1st line Tx : ImmunoTx + Etoposide/platinum CTx → ImunoTx maintenance
(IMPOWER 133, CASPIAN study)

2nd/3rd line Tx

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PRIMARY THERAPY FOR EXTENSIVE STAGE SCLC[c]:

Four cycles of cytotoxic chemotherapy are recommended, but some patients may receive up to 6 cycles based on response and tolerability after 4 cycles.

Preferred Regimens

- Carboplatin AUC 5 day 1 and etoposide 100 mg/m² days 1, 2, 3 and atezolizumab 1200 mg day 1 every 21 days x 4 cycles followed by maintenance atezolizumab 1200 mg day 1, every 21 days (category 1 for all)[d,e,k,6]
- Carboplatin AUC 5 day 1 and etoposide 100 mg/m² days 1, 2, 3 and atezolizumab 1200 mg day 1 every 21 days x 4 cycles followed by maintenance atezolizumab 1680 mg day 1, every 28 days[d,e,k]
- Carboplatin AUC 5–6 day 1 and etoposide 80–100 mg/m² days 1, 2, 3 and durvalumab 1500 mg day 1 every 21 days x 4 cycles followed by maintenance durvalumab 1500 mg day 1 every 28 days (category 1 for all)[d,e,f,7]
- Cisplatin 75–80 mg/m² day 1 and etoposide 80–100 mg/m² days 1, 2, 3 and durvalumab 1500 mg day 1 every 21 days x 4 cycles followed by maintenance durvalumab 1500 mg day 1 every 28 days (category 1 for all)[d,e,f,7]

Other Recommended Regimens

- Carboplatin AUC 5–6 day 1 and etoposide 100 mg/m² days 1, 2, 3[8]
- Cisplatin 75 mg/m² day 1 and etoposide 100 mg/m² days 1, 2, 3[9]
- Cisplatin 80 mg/m² day 1 and etoposide 80 mg/m² days 1, 2, 3[10]
- Cisplatin 25 mg/m² days 1, 2, 3 and etoposide 100 mg/m² days 1, 2, 3[11]

Useful in Certain Circumstances

- Carboplatin AUC 5 day 1 and irinotecan 50 mg/m² days 1, 8, 15[12]
- Cisplatin 60 mg/m² day 1 and irinotecan 60 mg/m² days 1, 8, 15[13]
- Cisplatin 30 mg/m² days 1, 8 and irinotecan 65 mg/m² days 1, 8[14]

Footnotes (SCL-E 2 of 6)
Subsequent Systemic Therapy (SCL-E 3 of 6)
Response Assessment (SCL-E 4 of 6)
References (SCL-E 5 of 6)

Summary

Extensive disease

1st line Tx : ImmunoTx + Etoposide/platinum CTx → ImunoTx maintenance
(IMPOWER 133, CASPIAN study)

2nd/3rd line Tx

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SCLC SUBSEQUENT SYSTEMIC THERAPY (PS 0–2)[g]
Consider dose reduction or growth factor support for patients with PS 2

CHEMOTHERAPY-FREE INTERVAL (CTFI) >6 MONTHS

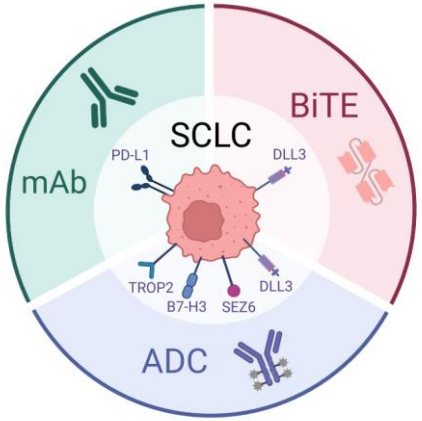
Preferred Regimens
- Clinical trial enrollment
- Re-treatment with platinum-based doublet[h,15-19]

Lurbinectedin; CTFI

Tarlatamab; Unfamiliar but manageable side effects (CRS, ICANS)

- Lurbinectedin[20,21]
- Topotecan oral (PO) or intravenous (IV)[17,22-25]
- Irinotecan[i,25,26]
- Tarlatamab-dlle[j,28]
- Re-treatment with platinum-based doublet may be considered for CTFI 3–6 months[h,17-19]

Other Recommended Regimens
- Nivolumab[k] or pembrolizumab (if not previously treated with an ICI)[d,29-33]
- Paclitaxel[34,35]
- Temozolomide[36,37]
- Cyclophosphamide/doxorubicin/vincristine (CAV)[22]
- Docetaxel[38]
- Gemcitabine[27,39,40]
- Oral etoposide[41,42]



의료에 신뢰를 더하다. JBUH+

감사합니다.

DeLLphi 301

Monitoring and Management of CRS and ICANS

AMGEN

Vital Sign Monitoring During Cycle 1 Per the DeLLphi-301 Study Protocol

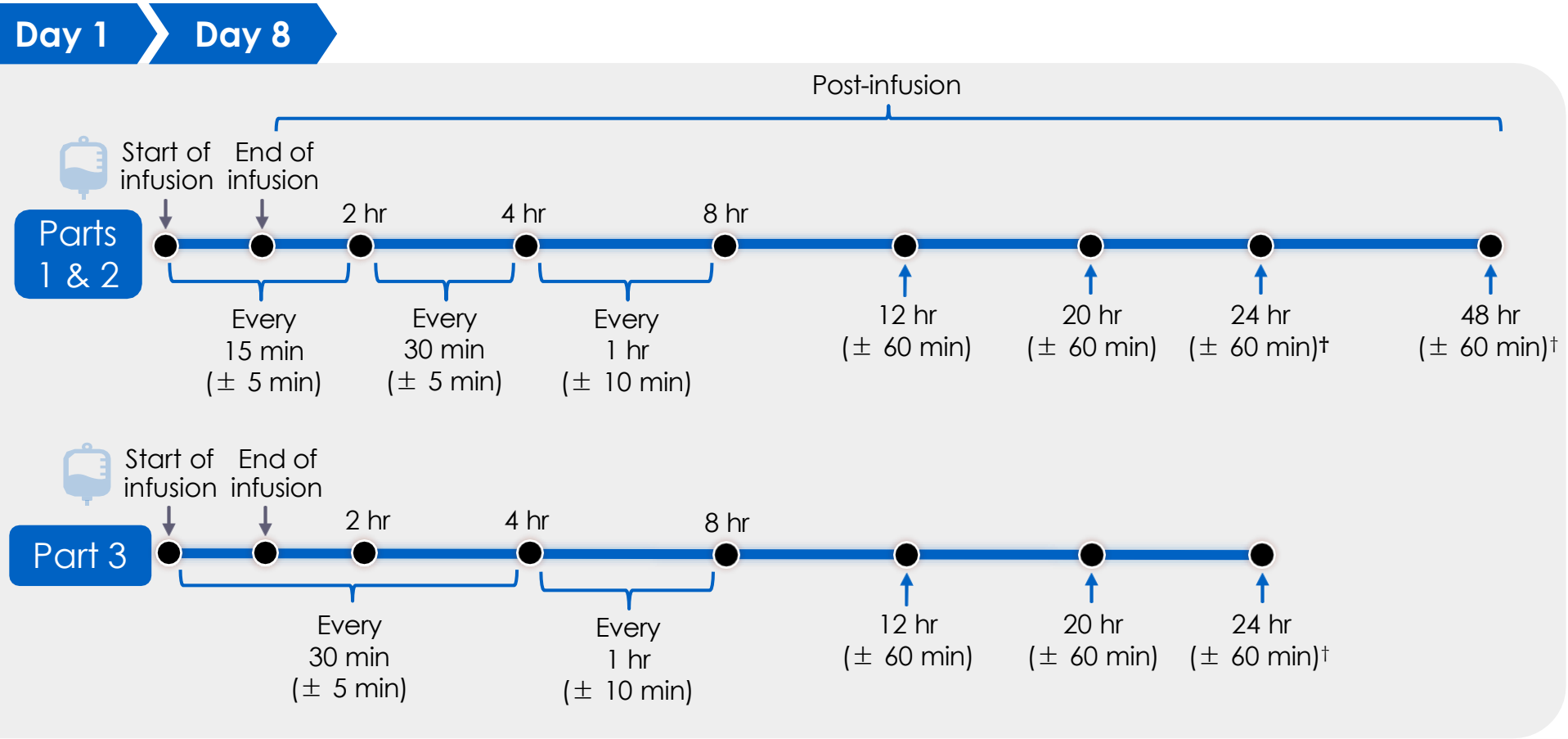
DeLLphi 301

Hospitalization*:

Part 1 & 2: Required 48 hours for days 1 and 8
Part 3: Required for 24 hours for days 1 and 8

Monitor:

- Temperature
- Respiratory rate
- Heart rate
- Blood pressure
- Oxygen saturation



*Hospitalization was not required for cycle 1 day 15 unless the patient experienced any grade CRS or neurologic events following days 1 or 8. If a patient was not hospitalized on day 15 of cycle 1, vital signs were only collected up to 6 to 8 hours. †After 24 hours post-infusion, vital signs were assessed per institutional standards.
CRS, cytokine release syndrome.
Ahn MJ, et al. *N Engl J Med*. 2023;389:2063-2075; Protocol.

AMGEN

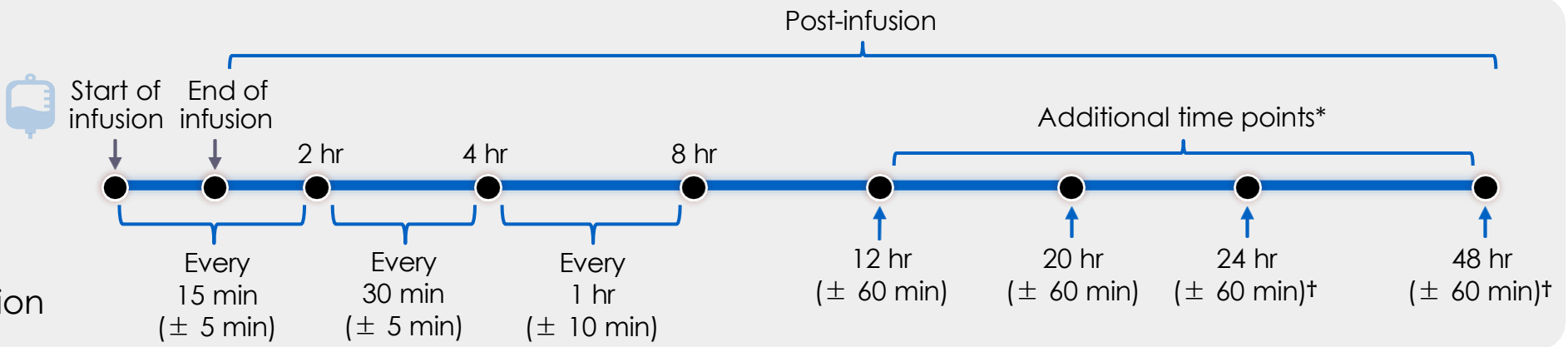
Vital Sign Monitoring During Cycle 2 Per the DeLLphi-301 Study Protocol

DeLLphi 301

Cycle 2 (All Parts)

Day 1 **Day 15**

Monitor:
- Temperature
- Respiratory rate
- Heart rate
- Blood pressure
- Oxygen saturation



- Hospitalization was not required for cycle 2 unless a patient experiences grade 2 or higher CRS or neurologic events in cycle 1
- If patients were not hospitalized during cycle 2, patients were observed for 8 hours post-infusion

*For patients requiring hospitalization. †After 24 hours post-infusion, vital signs were assessed per institutional standards.
CRS, cytokine release syndrome.
Ahn MJ, et al. *N Engl J Med*. 2023;389:2063-2075; Protocol.

AMGEN

CRS Management by Grade Per the DeLLphi-301 Study Protocol

DeLLphi 301

Management	Grade 1	Grade 2	Grade 3	Grade 4
General	• Symptomatic treatment (eg, paracetamol/acetaminophen) • Manage per grade 3 CRS for subjects with rapid onset (< 4 hours from start of infusion), extensive co-morbidities, or poor performance status		• Symptomatic treatment (eg, paracetamol/acetaminophen) • Dexamethasone (or equivalent) IV at a dose maximum of three doses of 8 mg (24 mg/d)*	
			AND/OR Consider use of tocilizumab†,‡,§	• Tocilizumab should be administered at a dose of 4-8 mg/kg as a single dose‡,§
Fever	• Antipyretics (eg, acetaminophen/paracetamol)			
Hypotension	NA	• IVF when systolic blood pressure is < 85 mmHg. Persistent tachycardia (eg, > 120 bpm) may also indicate the need for further intervention	• Vasopressor ± vasopressin, as needed	• Multiple vasopressors, as needed
Hypoxia	NA	• Supplemental oxygen when oxygen saturation is < 90% on room air (low-flow (≤ 6 L/min) nasal cannula or blow-by)	• Supplemental oxygen (high-flow nasal cannula (> 6 L/min), facemask, non-rebreather mask, or Venturi mask), as needed	• Supplemental oxygen (positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation), as needed

*The dose should then be reduced step-wise for grade 3. Further corticosteroid use should be discussed for grade 4.
†In countries where available. If used as additional therapy in this setting, 4–8 mg/kg is administered as a single dose.
‡Tocilizumab can be repeated for additional 3 doses with at least an 8-hour interval between doses.
§If tocilizumab is not available, siltuximab (an anti-IL-6 monoclonal antibody) may be used in the management of CRS, following the criteria outlined in this table. The recommended dose of siltuximab is 11 mg/kg administered over 1 hour as an IV infusion, consistent with the prescribing information for the treatment of multicentric Castleman's disease (Sylvant Prescribing Information), and the CARTOX Working Group Guidelines for CRS management (Neelapu et al, 2018). Siltuximab may be repeated if needed, in the event that CRS recurs after a subsequent infusion of tarlatamab. Siltuximab may not be repeated in an individual subject who develops anaphylaxis to siltuximab or gastrointestinal perforation after administration of siltuximab.
BiPAP, bi-level positive airway pressure; **CPAP**, continuous positive airway pressure; **CRS**, cytokine release syndrome; **IL**, interleukin; **IV**, intravenous; **IVF**, intravenous fluids; **NA**, no action.
Ahn MJ, et al. *N Engl J Med*. 2023;389:2063-2075; Protocol.

AMGEN

Tarlatamab Dose Modification Guideline for CRS Per the DeLLphi-301 Study Protocol

DeLLphi 301

	Grade 1	Grade 2	Grade 3	Grade 4
Dose Interruption/Delay	No action required	Delay tarlatamab until event improves to CRS grade ≤ 1	Delay tarlatamab until the event improves to CRS grade ≤ 1	
Restart Guidance		The next infusion may be administered if all of the following criteria are met: • The Amgen medical monitor must be consulted prior to restarting treatment • If CRS occurred during tarlatamab infusion, infusion has been interrupted for at least 72 hours • The event has resolved to grade ≤ 1 prior to restarting treatment		
Permanent Discontinuation		If there is no improvement to CRS ≤ grade 1 within 7 days	• If there is no improvement to CRS ≤ grade 2 within 5 days and CRS ≤ grade 1 within 7 days • If CRS grade 3 occurs at the initial dose • In the case of two separate grade 3 CRS events	Immediately stop the infusion (if applicable) and permanently discontinue tarlatamab

CRS, cytokine release syndrome.
Ahn MJ, et al. *N Engl J Med*. 2023;389:2063-2075; Protocol.

AMGEN

Tarlatamab Dose Modification Guidelines and Management for ICANS and Associated Neurologic Events Per the DeLLphi-301 Study Protocol

	Grade 1	Grade 2	Grade 3	Grade 4
Dose Interruption/Delay			Interrupt tarlatamab until the event improves to grade ≤ 1	Interrupt tarlatamab
Specific Management	Follow institutional guidelines		Administration of corticosteroids is permissible based on investigator judgment and local practice	
Restart Guidance			Resume tarlatamab no less than 72 hours after the initial observation of the grade 3 adverse event	
Permanent Discontinuation			Initial grade 3 neurologic event does not improve to grade ≤ 1 within 7 days OR Grade 3 neurologic event reoccurs within 7 days of re-initiation	Permanently discontinue

ICANS, immune effector cell-associated neurotoxicity syndrome.
Ahn MJ, et al. *N Engl J Med*. 2023;389:2063-2075; Protocol.

ICANS and Associated Neurologic Events Assessment and Supportive Care Guidance Per the DeLLphi-301 Study Protocol

	Grade 1	Grade 2*	Grade 3*	Grade 4*
No Concurrent CRS	• Supportive Care	• Supportive care • Dexamethasone (10 mg IV x 1) • Can repeat every 6 hours or methylprednisolone (1 mg/kg IV) every 12 hours, if symptoms worsen	• Supportive care • Dexamethasone (10 mg IV) every 6 hours or methylprednisolone (1 mg/kg IV) every 12 hours† • Consider repeat neuroimaging (CT or MRI) every 2–3 days if subject has persistent grade ≥ 3 neurotoxicity	• ICU care, consider mechanical ventilation for airway protection • High-dose corticosteroids†,‡ • Consider repeat neuroimaging (CT or MRI) every 2–3 days if subject has persistent grade ≥ 3 neurotoxicity • Treat convulsive status epilepticus per institutional guidelines
Additional therapy if Concurrent CRS	• In the setting of grade ≥ 3 CRS with hypotension, tocilizumab (8 mg/kg IV) over 1 hour • Not to exceed 800 mg/dose§	• Anti-IL-6 therapy as per grade 1§ • Consider transferring subject to ICU if neurotoxicity associated with grade ≥ 2 CRS	• Anti-IL-6 therapy as per grade 1§	

*Diagnostic lumbar puncture for grade 3–4 neurotoxicity; consider for grade 2. †Antifungal prophylaxis should be strongly considered in subjects receiving steroids for the treatment of CRS and/or neurotoxicity. ‡For example, methylprednisolone IV 1000 mg/day for 3 days, followed by rapid taper at 250 mg every 12 hours for 2 days, and 60 mg every 12 hours for 2 days. §Repeat tocilizumab every 8 hours as needed if not responsive to IV fluids or increasing supplemental oxygen. Limit to a maximum of three doses in a 24-hour period; maximum total of four doses.

CRS, cytokine release syndrome; **CT**, computed tomography; **ICANS**, immune effector cell–associated neurotoxicity syndrome; **ICU**, intensive care unit; **IL-6**, interleukin- 6; **IV**, intravenous; **MRI**, magnetic resonance imaging.

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