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GECP lung cancer research

New strategies in SCLC metastatic disease

Edurne Arriola MD, PhD

Hospital del Mar, Barcelona

Disclosures

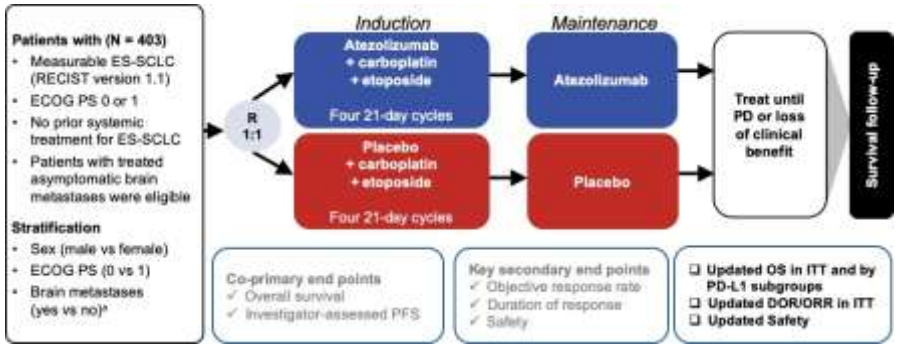
- Consultant or Advisor: MSD, Bristol-Myers, Roche, Boehringer Ingelheim, Pfizer, Novartis, AstraZeneca, Lilly, Takeda
- Speaker: MSD, Bristol-Myers, Roche, Boehringer Ingelheim, Pfizer, Novartis, AstraZeneca, Lilly, Takeda, Jansenn, Thermo Fisher, Guardant Health
- Co-founder: Trialing Health S.L

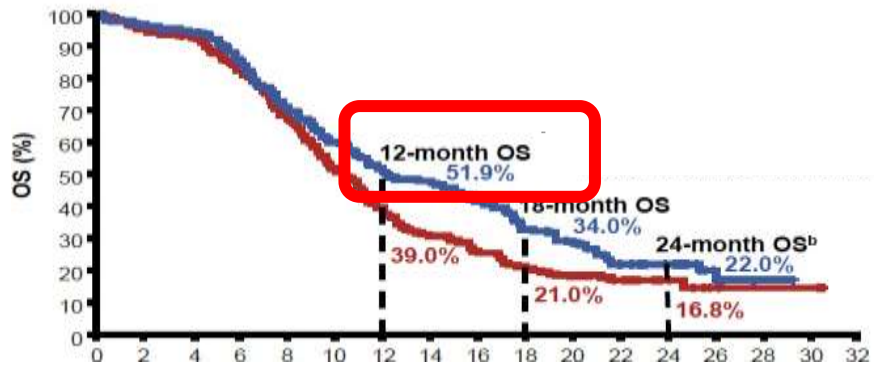
Outline

- Change in the SOC
- New strategies/new settings
  - DLL3 targeting agents
  - Antibody-drug conjugates
  - Other strategies
- Translational science

Standard of care in SCLC

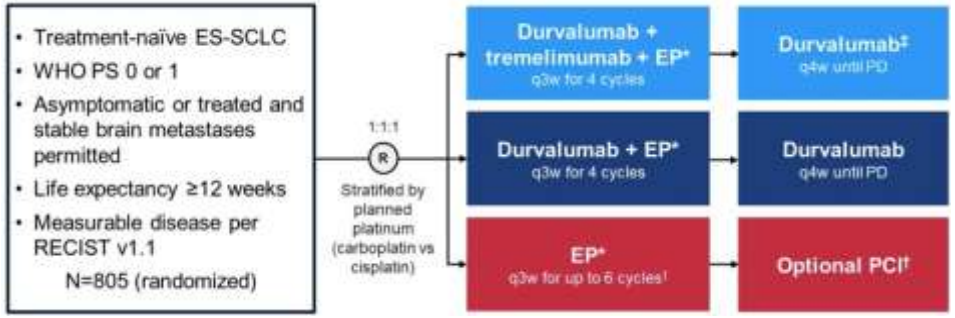
IMpower133

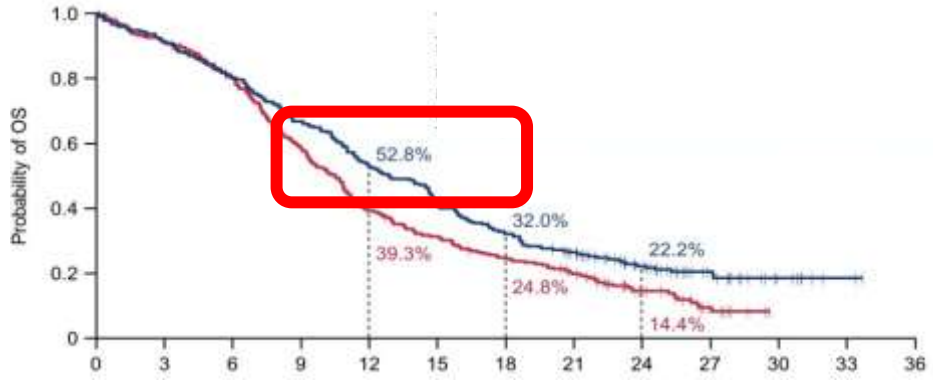




mOS 12.3 vs 10.3 mo
HR 0.76 (0.60, 0.95)
P = 0.0154

CASPIAN





mOS 12.9 vs 10.5 mo
HR 0.75 (0.62, 0.91)
P = 0.0032

Liu et al. ESMO 2020; Paz-Ares et al. ASCO 2020;

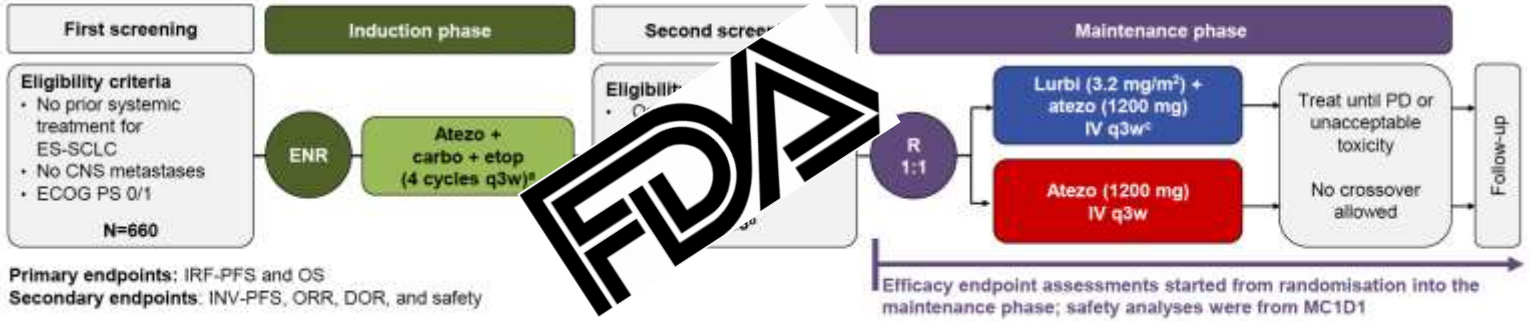
Trial	IMPOWER-133[1]	CASPIAN[2]	KN-604[3]	EA 5161[4]	ASTRUM[5]	CAPSTONE[6]	RATIONALE-312[7]
No. Of pts	403 (2 arms)	805 (3 arms)	453 (2 arms)	160 (2 arms)	585 (2 arms)	462 (2 arms)	456 (2 arms)
ICPI	Atezolizumab (anti PD-L1)	Durvalumab (anti PD-L1)	Pembrolizumab(anti PD-1)	Nivolumab (anti PD-1)	Serplulimab (anti PD-1)	Adebrelimab (anti PD-L1)	Tislelizumab(anti PD-1)
Platinum	Carboplatin	Carboplatin or cisplatin	Carboplatin or cisplatin	Carboplatin or cisplatin	Carboplatin	Carboplatin	Carboplatin or cisplatin
N of tx cycles	4 vs 4	4-6 (Ctrl) vs 4	4 vs 4	4 vs 4	4 vs 4	4-6 vs 4-6	4 vs 4
PCI/TRT	Yes/no	Yes(Ctrl) /no	Yes/no	Yes/no	No/no	Yes/no	-
Asian%	16	15	19	NR	68	100	100
RR%	64.4vs 60.2	58 vs 68	61.8 vs 70.6	47.5 vs 52.3	70.4 vs 80.2	65.0 vs 70.4	62 vs 68
mPFS (m)	4.3 vs 5.2 (p=0.02)	5.4 vs 5.1 (p=not tested)	4.3 vs 4.5 (p=0.002)	4.7 vs 5.5 (p=0.047)	4.3 vs 5.7 (p=not tested)	5.6 vs 5.8 (p=0.0001)	4.3 vs 4.7 (p<0.0001)
mOS(m)	10.3 vs 12.3 (p=0.007)	10.3 vs 13 (p=0.004)	9.7 vs 10.8 (p=0.016)NS	9.3 vs 11.3 (p=0.14)NS	10.9 vs 15.4 (p=0.001)	12.8 vs 15.3 (p=0.0017)	13.5 vs 15.5 (p=0.004)

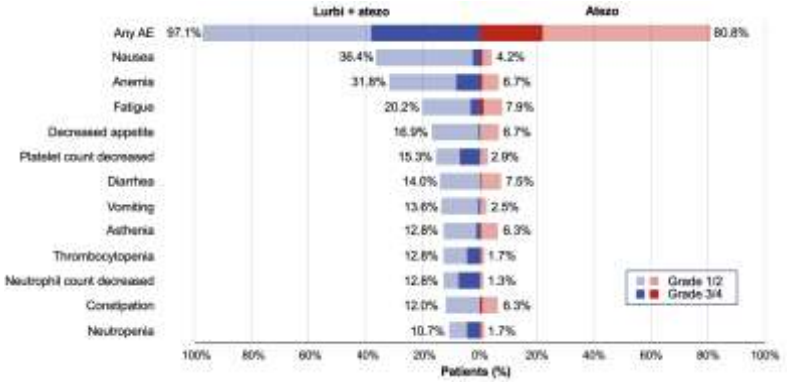
Extracted from 1) Horn L et al. N Engl J Med. 2018;379(23):2220-2229; 2) Paz Ares L et al. Lancet. 2019;394(10212):1929-1939; 3) Rudin CM et al. J Clin Oncol. 2020;38(21):2369-2379; 4) Leal TA et al. J Clin Oncol. 2020;38(15 suppl):9000; 5) Cheng Y et al. JAMA. 2022;328(12):1223–1232; 6) Wang J et al. Lancet Oncol. 2022 Jun;23(6):739-747; 7) Cheng Y et al. J Thorac Oncol. 2024;19(7):1073-1085.

Recent changes in the SOC - Imforte-Lurbinectedine in maintenance

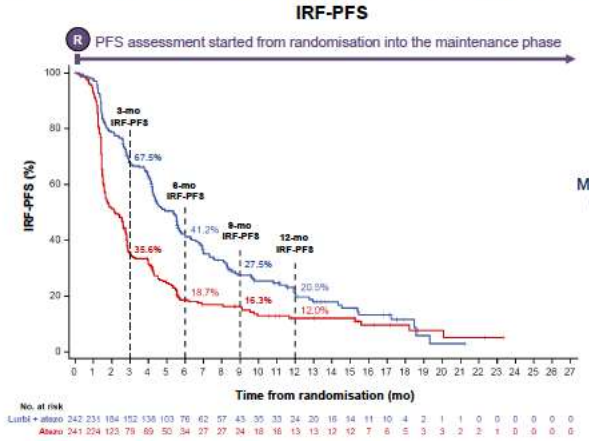
Background and study design

- IMforte is the first Phase 3 study to demonstrate statistically significant and clinically meaningful improvements in PFS and OS with lurbi + atezo vs atezo for 1L maintenance treatment of ES-SCLC

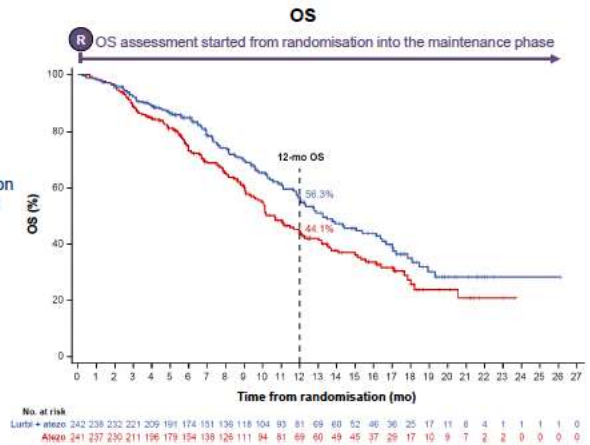




IRF-PFS and OS from randomisation into maintenance phase

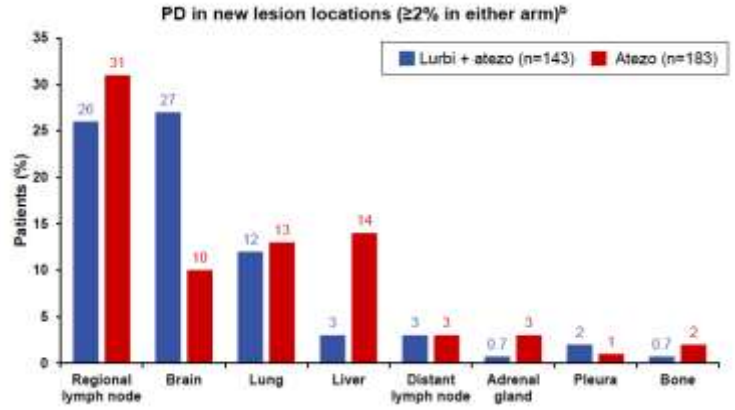


Median time from induction C1D1 to randomisation: 3.2 mo in each arm



IRF-PFS	Lurbi + atezo (n=242)	Atezo (n=241)
Events, n (%)	174 (71.9)	202 (83.8)
PFS, median (95% CI), mo	5.4 (4.2, 5.8)	2.1 (1.6, 2.7)
Stratified HR (95% CI)	0.54 (0.43, 0.67)	
Stratified *P* value (2-sided)	<0.0001	
α boundary (2-sided)	0.001	

OS	Lurbi + atezo (n=242)	Atezo (n=241)
Events, n (%)	113 (46.7)	136 (56.4)
OS, median (95% CI), mo	13.2 (11.9, 16.4)	10.6 (9.5, 12.2)
Stratified HR (95% CI)	0.73 (0.57, 0.95)	
Stratified *P* value (2-sided)	0.0174	
α boundary (2-sided)[a]	0.0313	



Paz-Ares et al. Lancet and ESMO 2025

Recent changes in the SOC – Dellphi-304- Tarlatamab in 2nd line

Key inclusion criteria

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

Randomization stratified by

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

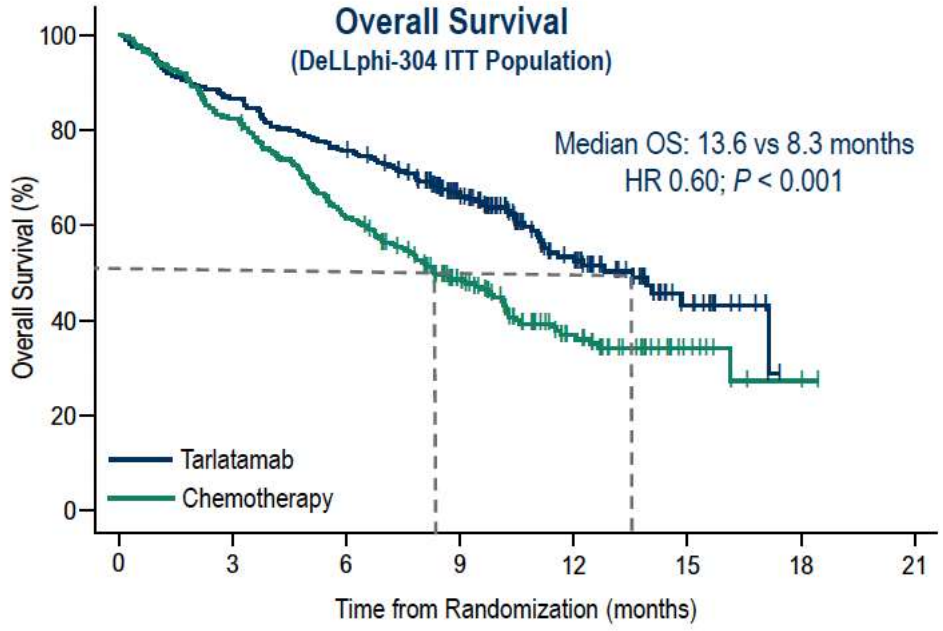
R
1:1
(N = 509)

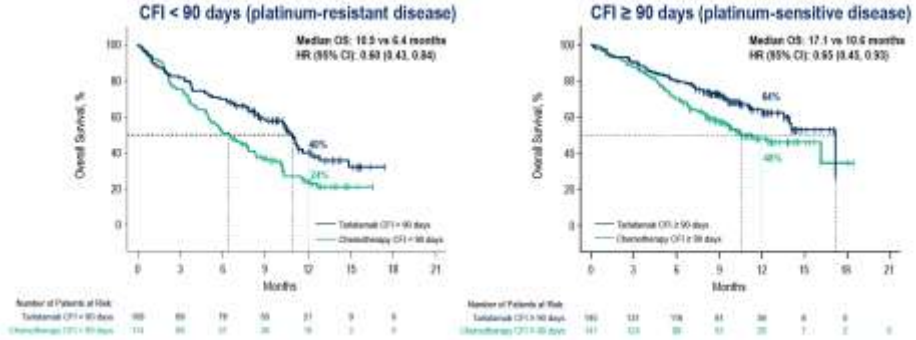
Tarlatamab (n = 254)

Chemotherapy* (n = 255)

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

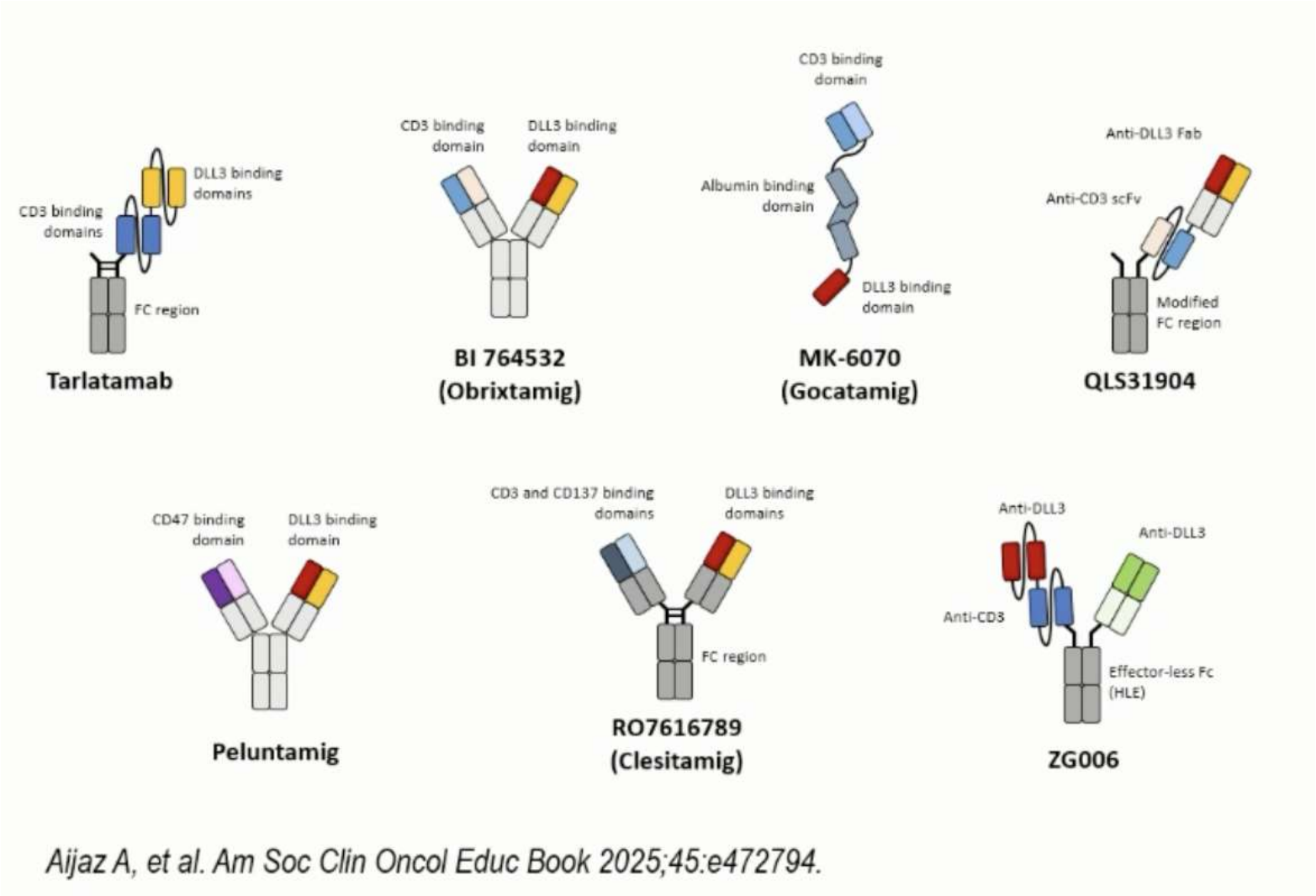
Primary Endpoint: Overall survival
Secondary Endpoints: Progression-free survival, patient-reported outcomes, objective response rate, safety



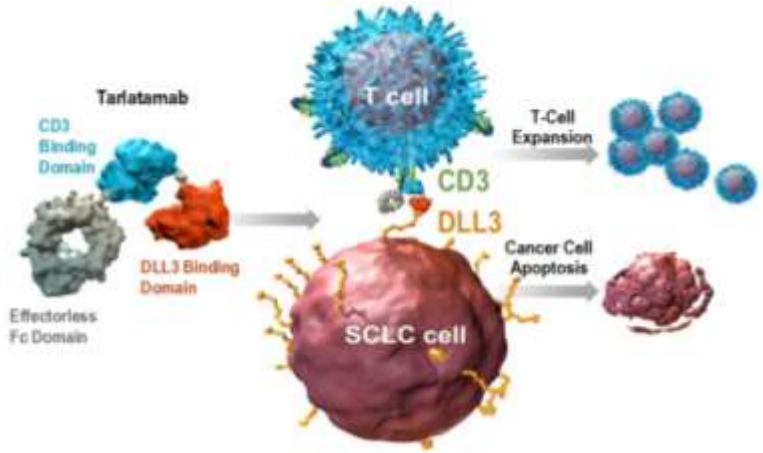


Mountzious et al. NEJM 2025; Rocha et al. ESMO 2025

DLL3 targeting T cell engagers



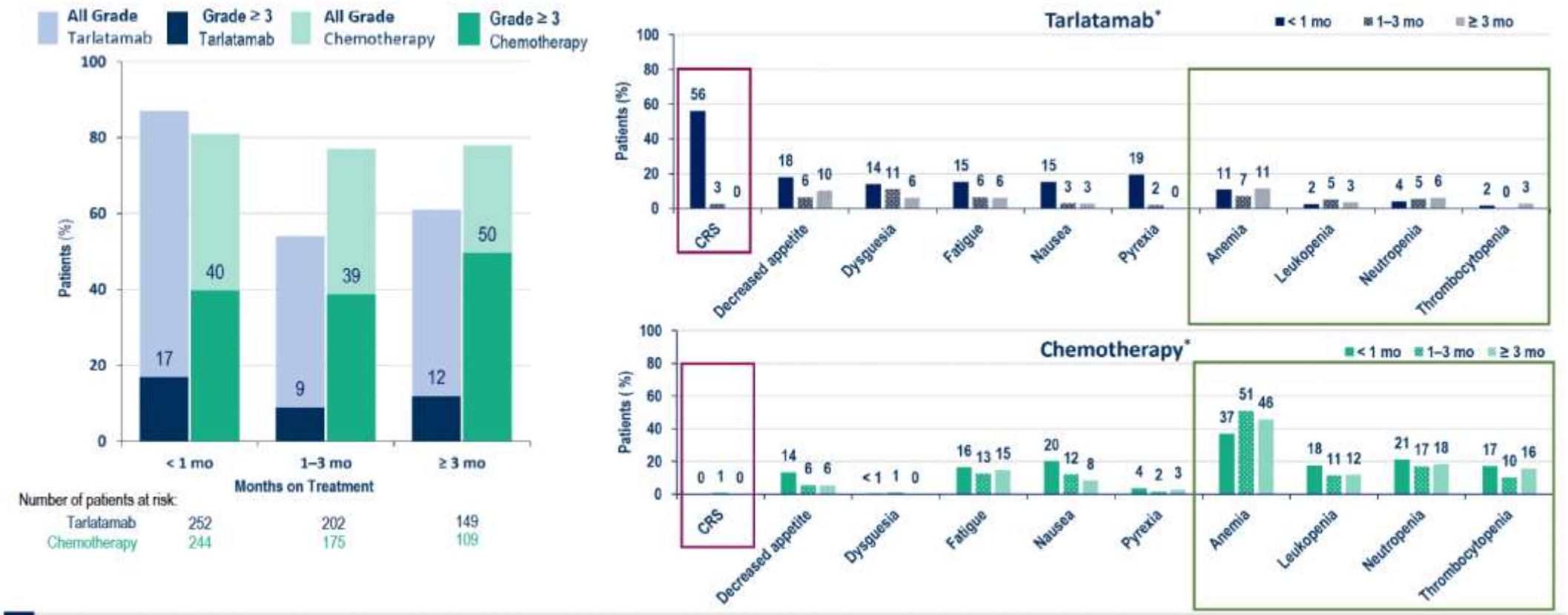
Aijaz A, et al. Am Soc Clin Oncol Educ Book 2025;45:e472794.



Rudin et al. Journal of Hematology & Oncology, 2023

Toxicity management

Incidence and Severity of Treatment-related Adverse Events Over Time



- Tarlatamab TRAEs decreased over time and grade ≥ 3 TRAEs remained lower compared to chemotherapy
- CRS occurred predominately in cycle 1 with tarlatamab; chemotherapy showed persistent hematologic toxicities across time

Schuler et al. ESMO 2025

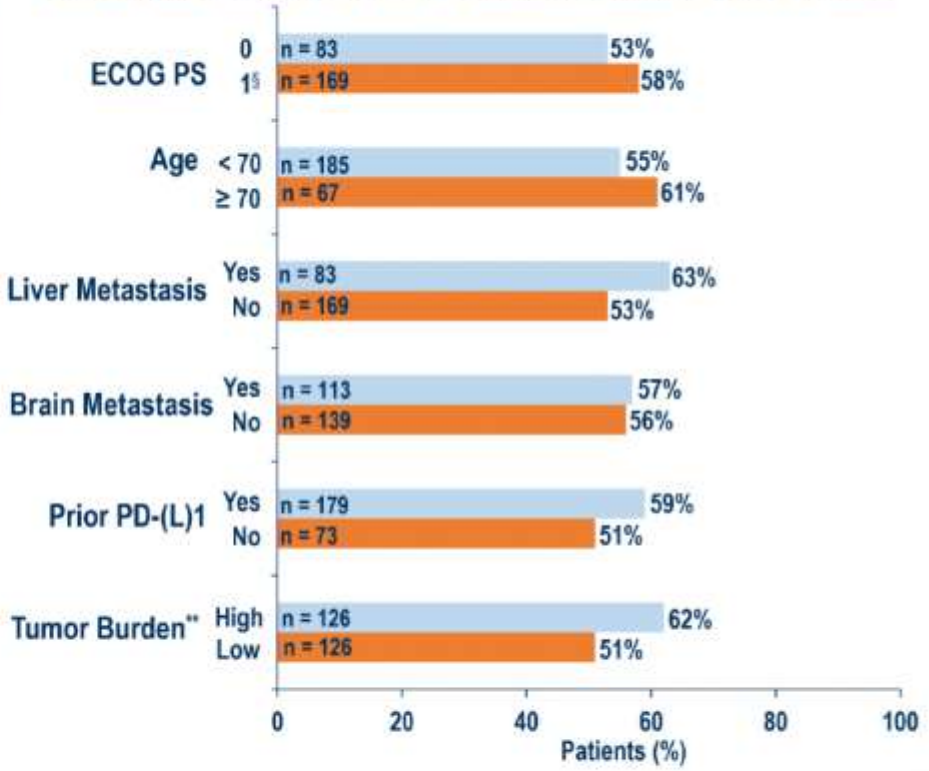
Toxicity management

CRS Dynamics and Monitoring Insights for Tarlatamab

Treatment-related CRS During First Two Doses of Tarlatamab

Tarlatamab (n = 252)	Minimum Required Monitoring Duration	
	6–8 Hours (n = 43)	48 Hours (n = 209)
Treatment-related CRS (all grade), n (%)	16 (37)	125 (60)
Grade 1	12 (28)	94 (45)
Grade 2	4 (9)	28 (13)
Grade 3*	0	3 (1)
Leading to discontinuation	0	1 (0.5)
Utilization of any CRS intervention	9 (21)	45 (22)
Median time to intervention, hours	17	27
Hospitalization for any grade†	3 (7)	16 (8)
Patients with any resolved event‡, n/n' (%)	16/16 (100)	123/125 (98)

Descriptive Analysis of Treatment-related CRS Events



- **CRS with tarlatamab was predominantly grades 1 or 2 and occurred mainly in cycle 1**
- **No substantial differences in CRS rates were observed across examined subgroups**

*All events were grade 3 with no grade 4 or 5 events reported. †In Cycle 1, day 1 and cycle 1, day 8 combined. ‡Incidence of any resolved CRS event was calculated using the number of patients reporting CRS, (n'), as denominator. §After screening, the ECOG performance status score declined to 2 in two patients before the administration of treatment (baseline). **High tumor burden was defined as baseline SLD ≥ 71.955 mm of target lesions, low tumor burden was defined as baseline SLD < 71.955 mm of target lesions.

CRS, cytokine release syndrome; **ECOG PS**, Eastern Cooperative Oncology Group Performance Status; **PD-(L)1**, programmed death (ligand) 1; **SLD**, sum of diameter.

Schuler et al. ESMO 2025

Toxicity management

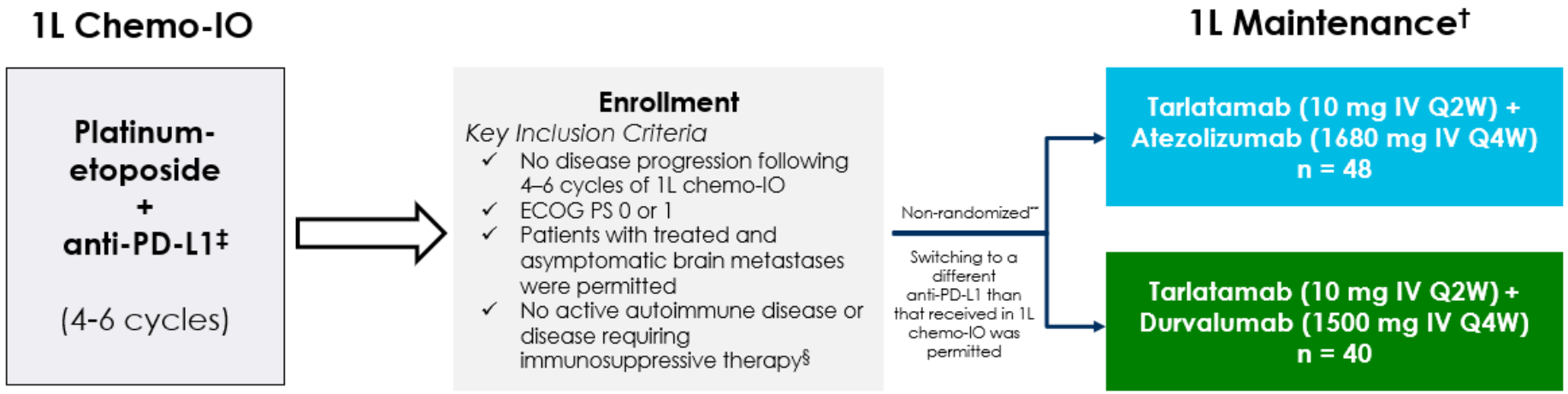
Practical management of adverse events in patients receiving tarlatamab, a delta-like ligand 3–targeted bispecific T-cell engager immunotherapy, for previously treated small cell lung cancer

Jacob M. Sands MD[1] | Stéphane Champiat MD, PhD[2] | Horst-Dieter Hummel MD[3] | Kelly G. Paulson MD, PhD[4] | Hossein Borghaei DO[5] | Jean Bustamante Alvarez MD[6] | David P. Carbone MD, PhD[7] | Jennifer W. Carlisle MD[8] | Noura J. Choudhury MD[9] | Jeffrey M. Clarke MD[10] | Shirish M. Gadgeel MD[11] | Hiroki Izumi MD, PhD[12] | Alejandro Navarro MD[13] | Sally C. M. Lau MD[14] | Philip E. Lammers MD[15] | Shuang Huang PhD[16] | Ali Hamidi MD[16] | Sujoy Mukherjee MD[16] | Taofeek K. Owonikoko MD, PhD[17]

Schuler et al. ESMO 2025; Sands et al. Cancer 2025

Tarlatamab-maintenance setting

Phase 1b study of tarlatamab with anti-PD-L1 as 1L maintenance for ES-SCLC: DeLLphi 303 Study*



Primary Endpoints††: Dose-limiting toxicities‡‡, treatment-emergent and treatment-related adverse events
Secondary Endpoints§§: Progression-free survival, overall survival, objective response rate, duration of response, and disease control

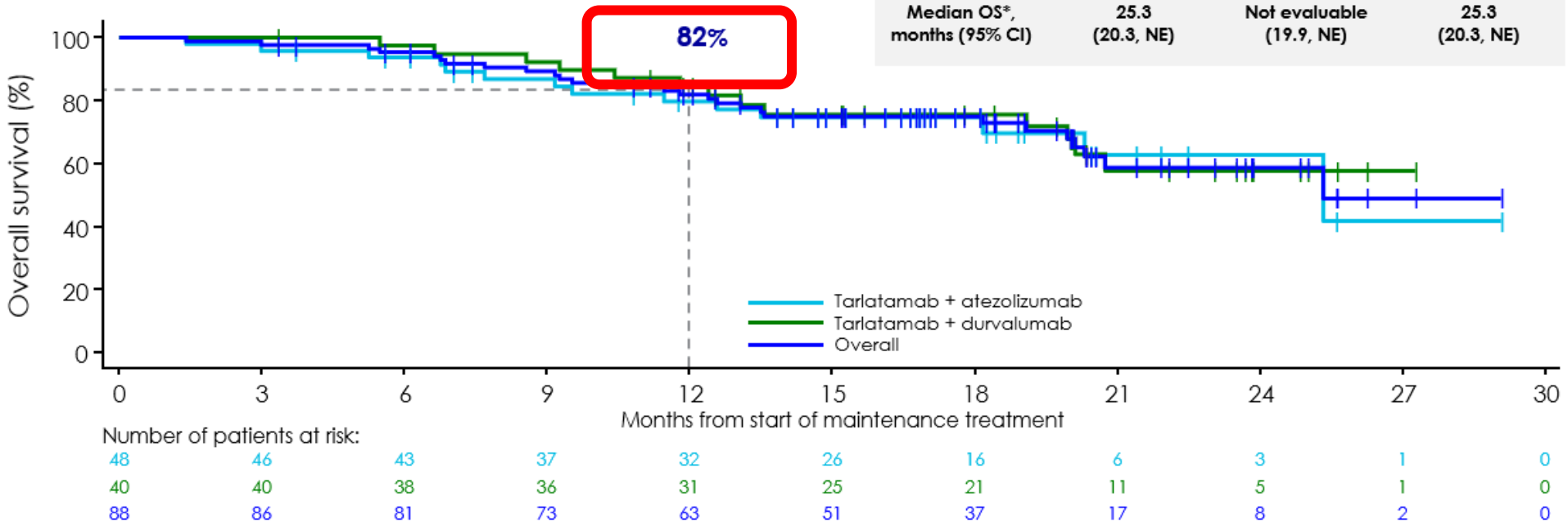
*Cohorts 5, 6, and 8; NCT05361395. †Maintenance therapy commenced within 8 weeks of the start of the last cycle of 1L chemo-IO. ‡Patients without access to 1L anti-PD-L1 were allowed. §Patients with active autoimmune disease requiring systemic treatment (except replacement therapy) within the past 2 years were excluded. **Patients were allocated to treatment arms in a non-randomized manner based on slot availability. ††Also included vital signs, electrocardiograms, and clinical laboratory tests. ‡‡DLTs were assessed for cohort 5 only. §§Also included serum concentrations of tarlatamab, quantification of biomarker expression, and incidence of anti-tarlatamab antibody formation.
1L: first-line; **chemo-IO:** chemotherapy-immunotherapy; **DLT:** dose-limiting toxicity; **ECOG PS:** Eastern Cooperative Oncology Group performance status; **ES-SCLC:** extensive-stage small cell lung cancer; **IV:** intravenous; **PD-L1:** programmed death-ligand 1; **Q2W:** once every 2 weeks; **Q4W:** once every 4 weeks.

Presented at the IASLC 2025 World Conference on Lung Cancer (WCLC). September 6-9, 2025; Barcelona, Spain.

Paulson et al. WCLC 2025

Overall survival with addition of tarlatamab to anti-PD-L1 as 1L maintenance therapy

	Tarlatamab+ Atezolizumab	Tarlatamab+ Durvalumab	Overall Tarlatamab + Anti-PD-L1
Median OS*, months (95% CI)	25.3 (20.3, NE)	Not evaluable (19.9, NE)	25.3 (20.3, NE)



With a median follow-up time of 18.4 months, tarlatamab with anti-PD-L1 as 1L maintenance therapy led to a median OS of 25.3 months (95% CI, 20.3, NE).

*The median OS is immature and will continue to evolve with longer follow-up time.
1L: first-line; **CI:** confidence interval; **NE:** not evaluable; **OS:** overall survival; **PD-L1:** programmed death-ligand 1.

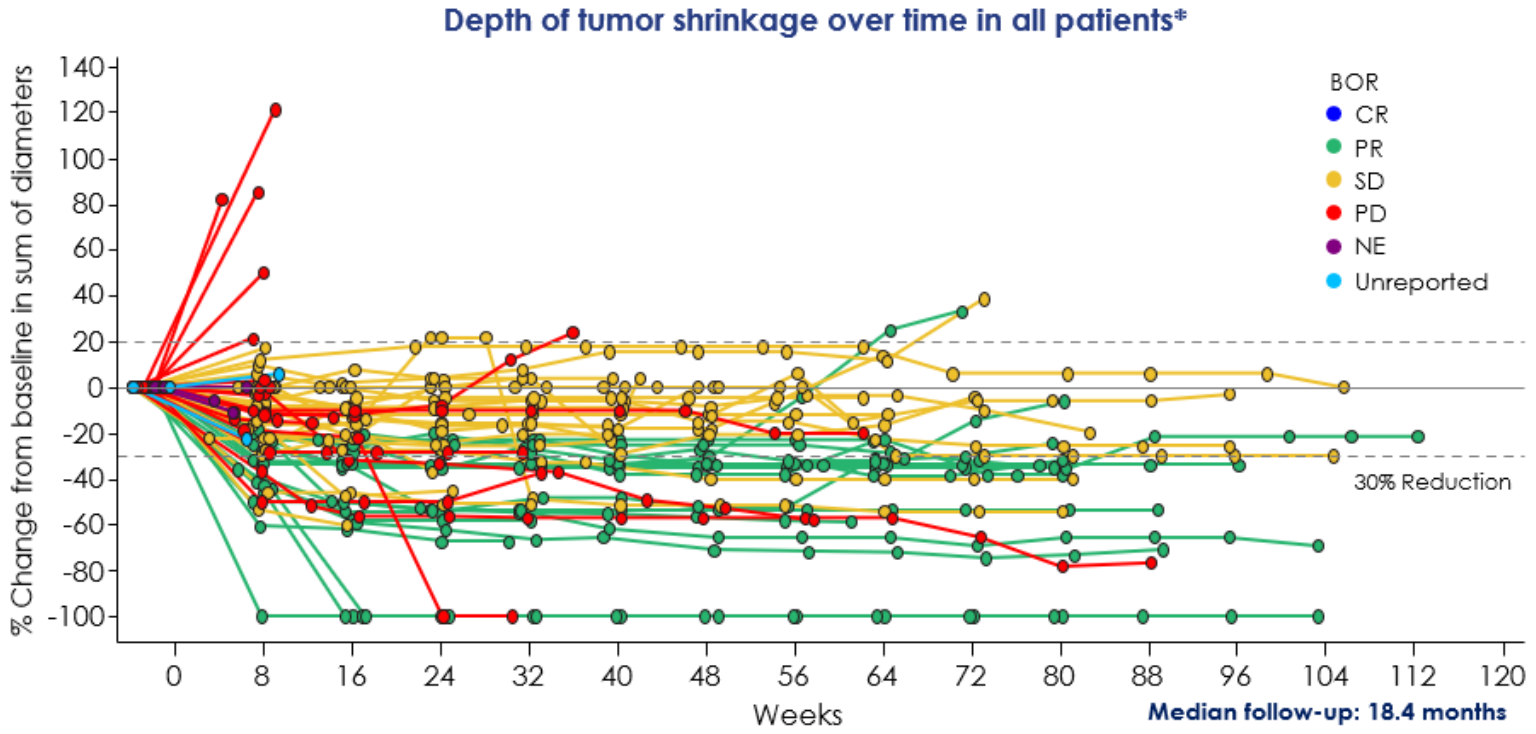
Presented at the IASLC 2025 World Conference on Lung Cancer (WCLC). September 6-9, 2025; Barcelona, Spain.

Paulson et al. WCLC 2025

Tarlatamab + anti-PD-L1 in 1L maintenance resulted in disease control in 60% of patients, including 36% with sustained disease control ≥ 52 weeks

From a baseline obtained after completion of 1L chemo-IO:

- Overall ORR: 24% (2 CR, 19 PR); median duration of response: 16.6 months (7.1, NE)
- Overall DCR: 60% (2 CR, 19 PR, 32 SD); median duration of disease control: 14.6 months (95% CI 7.2, 18.4)
- 24% of patients remained on treatment at data cutoff and 36% of patients showed sustained DC ≥ 52 weeks



*Fifteen patients did not have tumor size information and are not included in the spider plot. This includes two patients with non-target lesions who achieved CR during maintenance therapy with tarlatamab + anti-PD-L1.
1L: first-line; **BOR:** best overall response; **chemo IO:** chemo-immunotherapy; **CI:** confidence interval; **CR:** complete response; **DC:** disease control; **DCR:** disease control rate; **NE:** not evaluable; **ORR:** objective response rate; **PD:** progressive disease; **PD-L1:** programmed death-ligand 1; **PR:** partial response; **SD:** stable disease.

Presented at the IASLC 2025 World Conference on Lung Cancer (WCLC). September 6-9, 2025; Barcelona, Spain.

Paulson et al. WCLC 2025

Tarlatamab-1L setting

Phase 1b DeLLphi-303 study[a]

DeLLphi 303

1 Cycle of SOC

1L Chemo-IO

Platinum-etoposide + Anti-PD-L1[b]

ENROLLMENT

Key Inclusion Criteria

- ✓ Adults with ES-SCLC who **received 1 cycle of chemo-IO** (Enrollment allowed regardless of response to 1 cycle of chemo-IO)
- ✓ Measurable disease by modified RECIST 1.1
- ✓ ECOG PS 0 or 1
- ✓ Patients with treated, asymptomatic brain metastases were allowed
- ✓ No active autoimmune disease or disease requiring immunosuppressive therapy[c]

STUDY TREATMENT

1L Chemo-IO + Tarlatamab
Cycles 1-3

Tarlatamab
20 mg IV Q3W[d]
+
Platinum-etoposide
Carboplatin to match AUC 5 IV on day 1
etoposide 100 mg/m² on days 1-3
+
Anti-PD-L1[e]
Atezolizumab: 1200 mg IV Q3W
OR
Durvalumab: 1500 mg IV Q3W

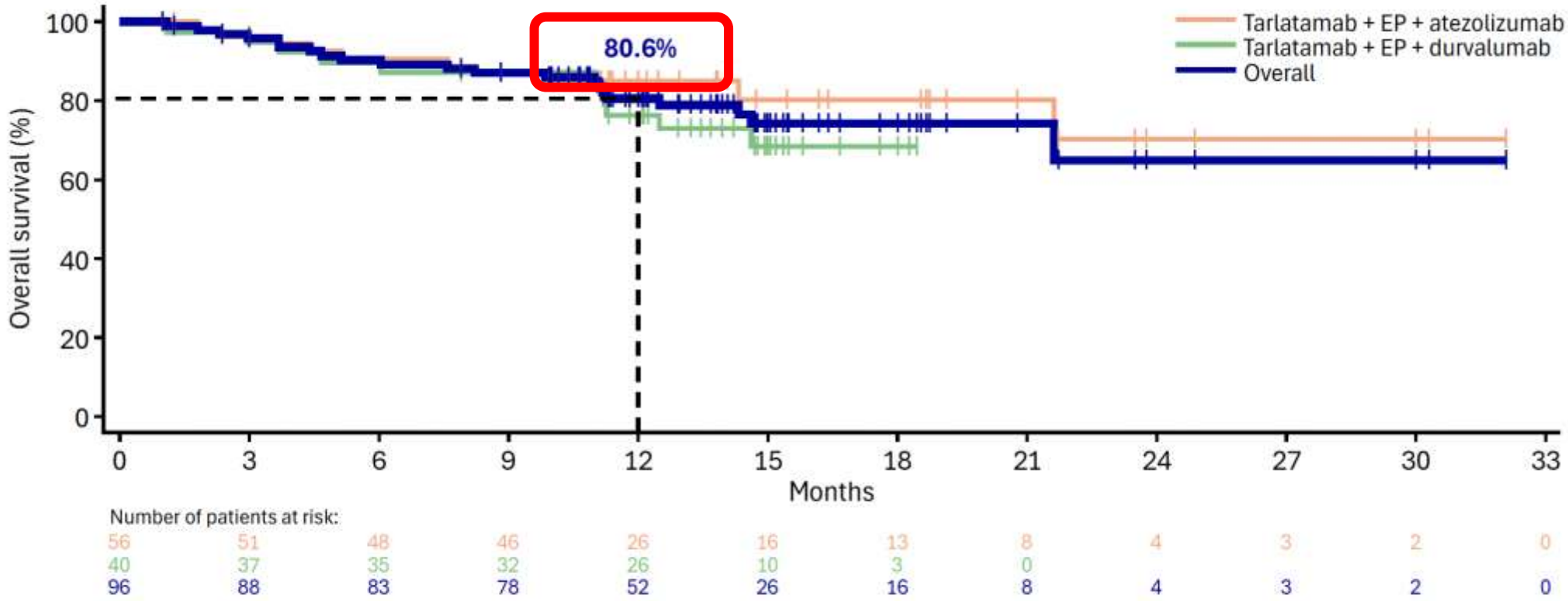
1L Maintenance
Cycles 4+

Tarlatamab
20 mg IV Q3W
+
Anti-PD-L1
Atezolizumab: 1200 mg IV Q3W
OR
Durvalumab: 1500 mg IV Q3W

Treatment until progressive disease[f]

Primary Endpoints[g]: Dose-limiting toxicities[h], treatment-emergent and treatment-related adverse events
Secondary Endpoints[i]: Objective response, duration of response, disease control, PFS, and OS

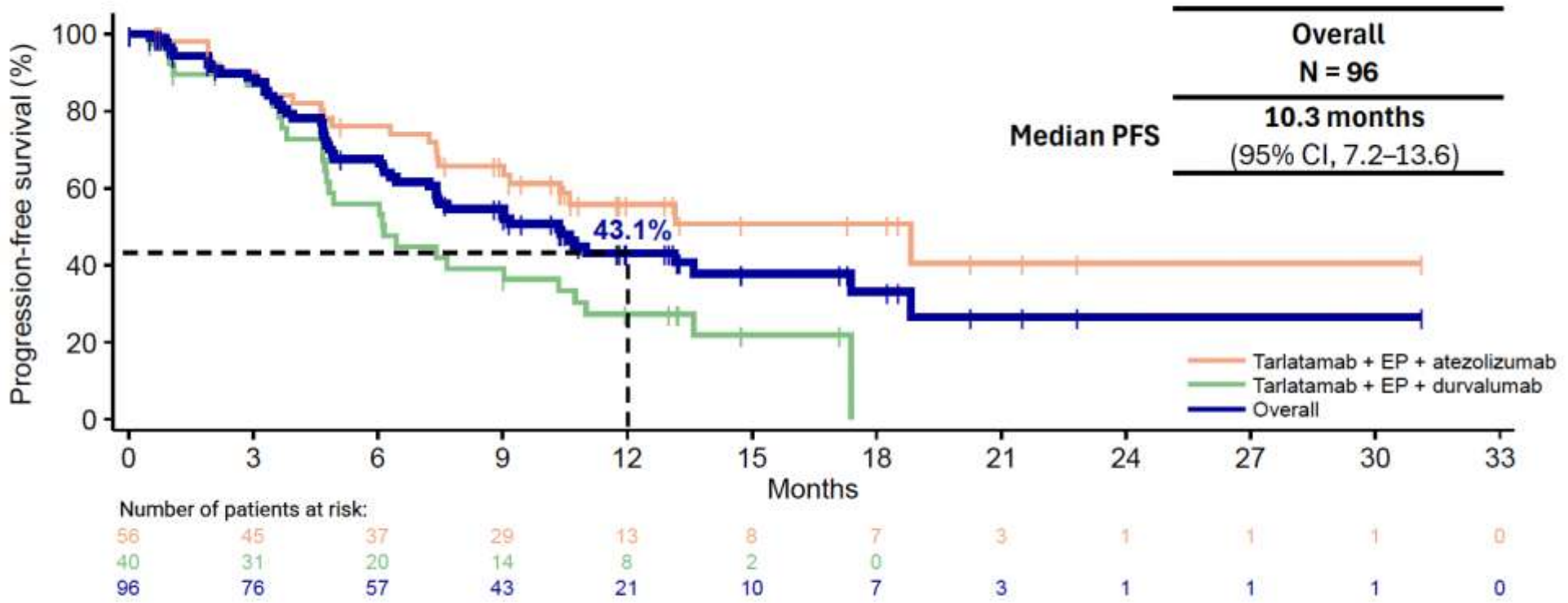
Overall survival with tarlatamab in combination with 1L SOC chemo-IO[a]



Median study follow-up: 13.8 months

- **Starting from the first dose of study treatment, the Kaplan-Meier estimate of OS at 12 months was 80.6%.**
- **The median OS was not yet estimable.**

Progression-free survival with tarlatamab in combination with 1L SOC chemo-IO[a]

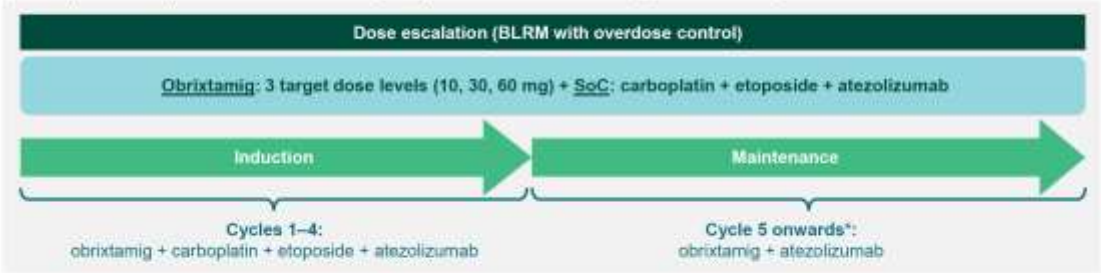


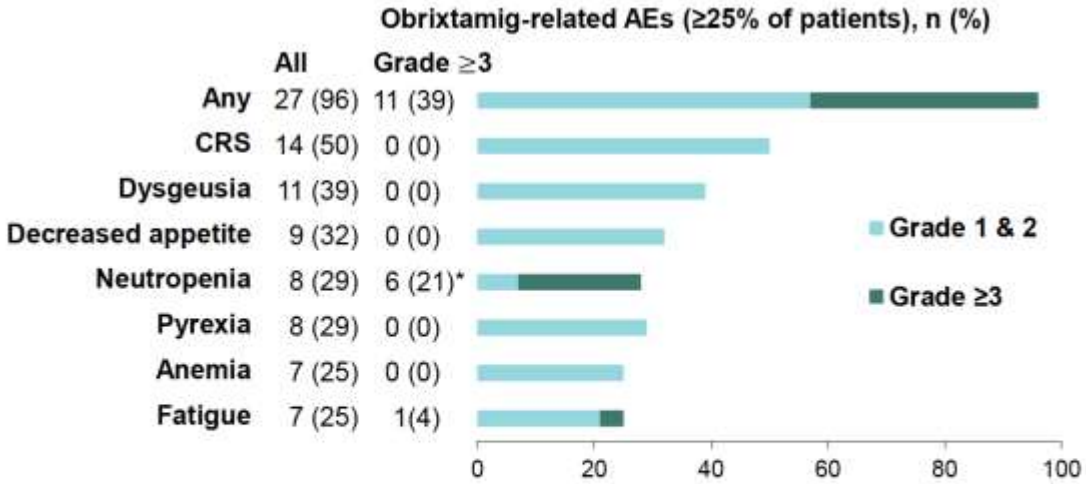
- Starting from the first dose of study treatment, the median PFS was 10.3 months
- The Kaplan-Meier estimate of PFS at 12 months was 43.1% (95% CI, 32.0– 53.7)

Obrixtamig-1L setting

DAREON®-8: a phase I trial of first-line obrixtamig plus SoC in both induction and maintenance

- DAREON®-8 is an ongoing dose-escalation/expansion trial investigating obrixtamig + first-line SoC (carboplatin + etoposide + atezolizumab) in patients with ES-SCLC (NCT06077500)





CRS was mostly grade 1 (no grade ≥3)

Grade 1	29%	n=8
Grade 2	21%	n=6

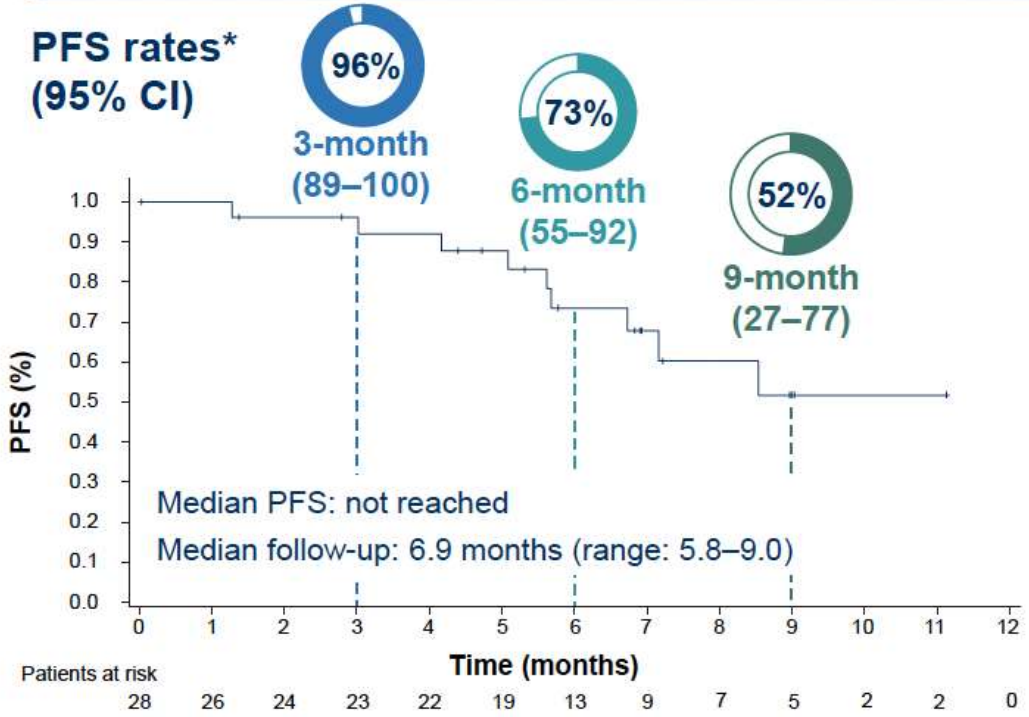
No grade ≥3 ICANS

Grade 1	4%	n=1
Grade 2	4%	n=1

- Seven patients (25%) had obrixtamig-related potential neurologic toxicities† including ICANS, with reported preferred terms of muscle spasms (grade 1, 11%), ICANS (grade 1–2, 7%), confusional state (grade 2, 4%), and dizziness (grade 1, 4%)
- Only one case of grade 2 neutropenia was attributed solely to obrixtamig. Primary prophylaxis with G-CSF was not allowed in the dose escalation part of the trial

Peters et al. ESMO 2025

Obrixtamig in combination with SoC showed estimated 6- and 9-month PFS rates* of 73% and 52%, respectively



Confirmed ORR†	**68%**	**(95% CI: 49–82)**
Confirmed DCR†	**89%**	**(95% CI: 73–96)**
Median DoR	7.3 months (95% CI: 4.4–NC)	

Best confirmed response, n (%)	N=28
CR	1 (4)
PR	18 (64)
SD	6 (21)
PD	1 (4)
NE / missing	2 (7)

Peters et al. ESMO 2025

Other DLL3 targeting strategies: TriTEs, CAR-T, radioligands

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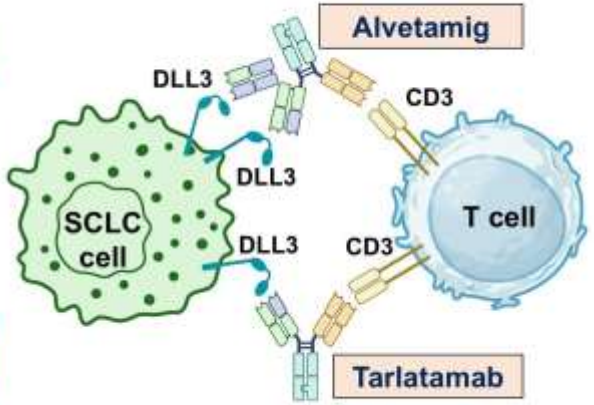
Alveltamig: DLL3 tri-specific TCE

	10 mg Q2W (N=24)	30 mg Q2W (N=24)
BOR		
CR, n (%)	0	0
PR, n (%)	15 (62.5)	14 (58.3)
SD, n (%)	2 (8.3)	2 (8.3)
PD, n (%)	6 (25.0)	6 (25.0)
NE, n (%)	1 (4.2)	2 (8.3)
ORR[1], n (%) 95% CI	15 (62.5) (40.6, 81.2)	14 (58.3) (36.6, 77.9)
DCR[1], n (%) 95% CI	17 (70.8) (48.9, 87.4)	16 (66.7) (44.7, 84.4)

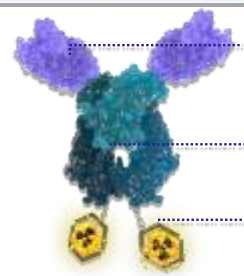


Is TriTE > BiTE?
Small numbers, more data needed

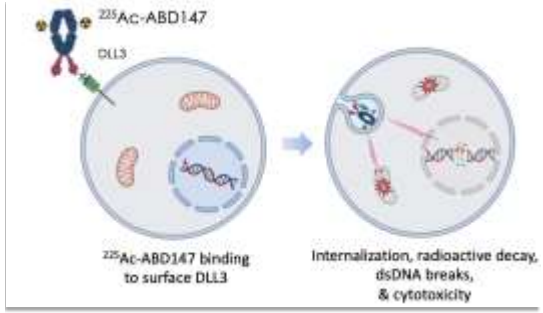
Ai et al. ASCO 2025 Abstract 8007

^{225}Ac-ABD147 and DLL3

ABD147 is a molecule engineered by Abdera's proprietary **Radio Optimized Vector Engineering (ROVER™)** platform

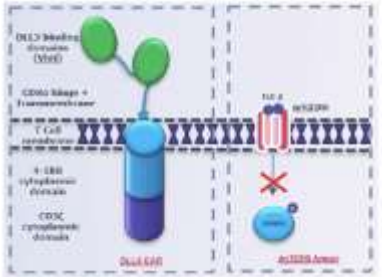


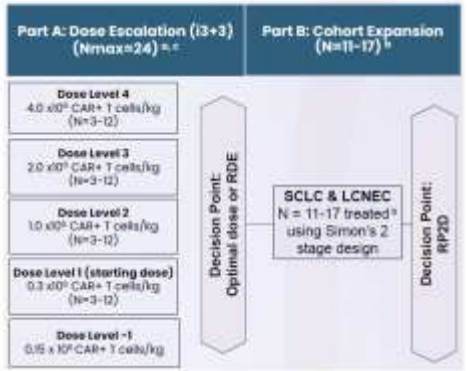
ABD147 binds **DLL3** with high affinity and specifically delivers targeted **^{225}Ac** to DLL3 positive cancer cells

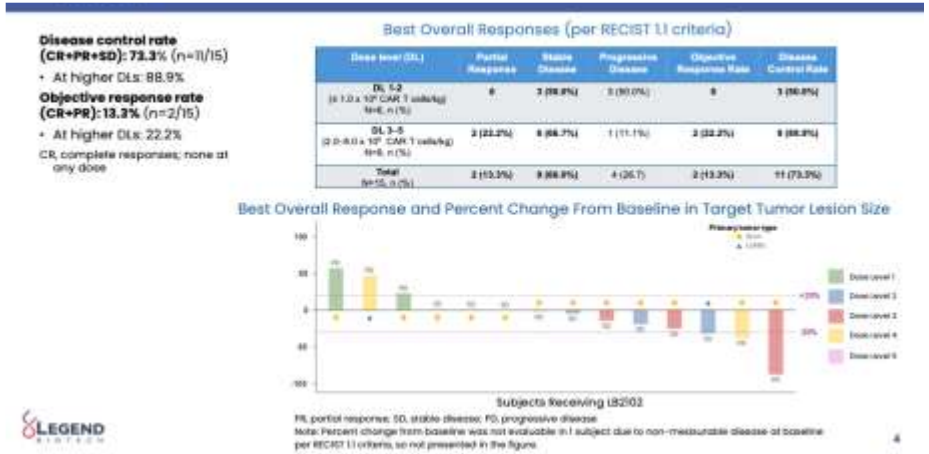


Chimeric Antigen Receptor-T cell: LB2102

-The dnTGF-βRII armor inhibits the TGFβ1-TGFβR pathway in LB2102 CAR-T cells.
-Armored LB2102 cells overcome TGFβ1-induced growth inhibition and maintain proliferation.

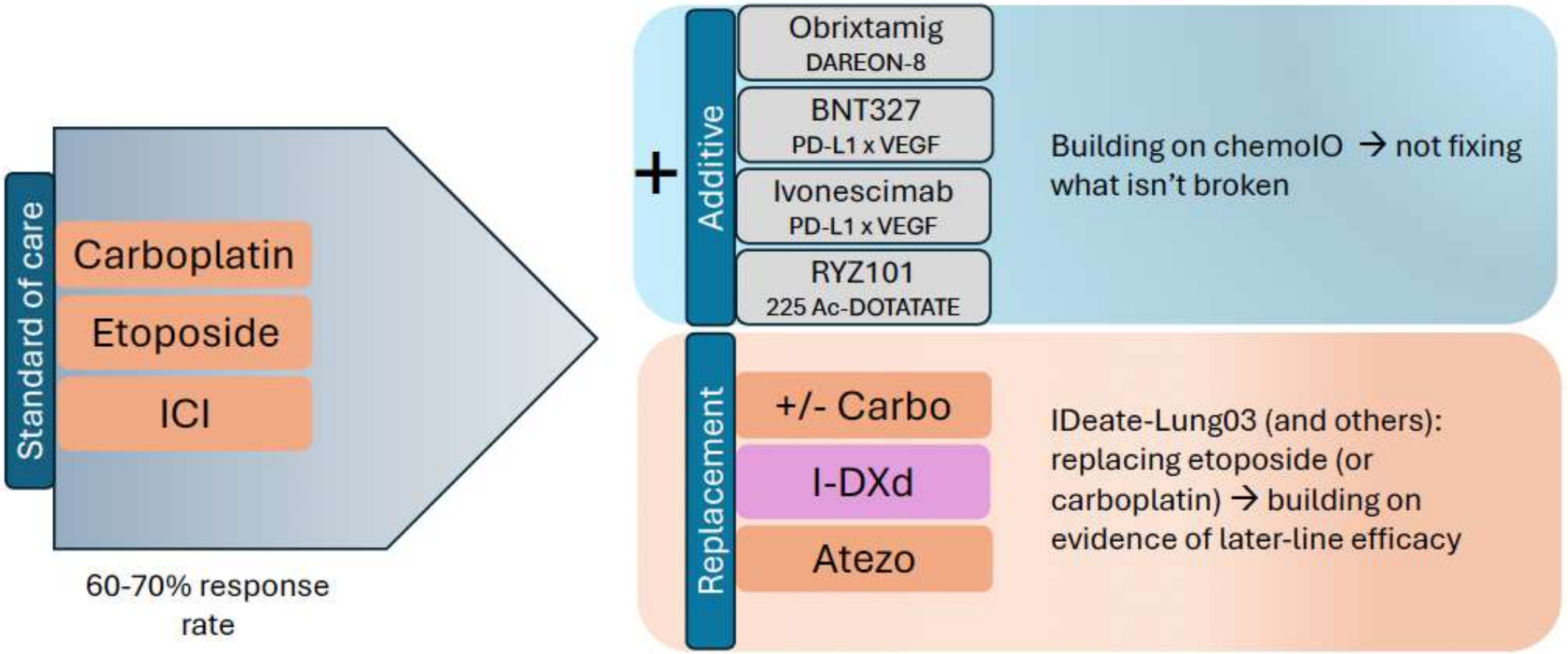






Sands et al. SITC 2024, Schoenfeld et al. WCLC 2025

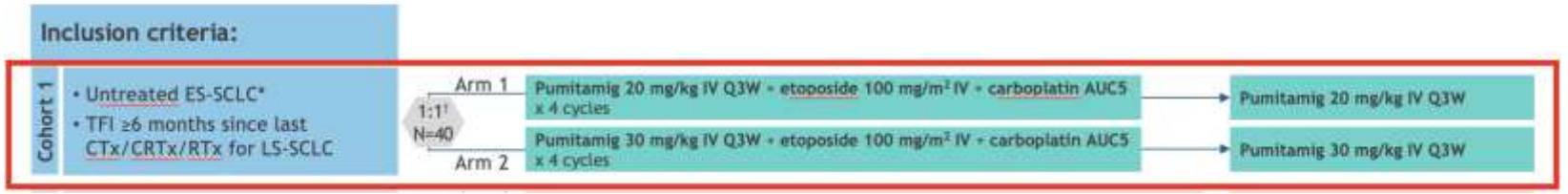
New strategies-challenging the first line setting

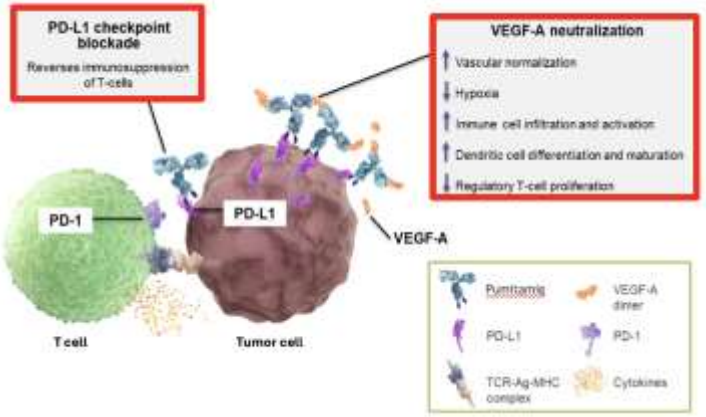


Choudhury WCLC 2025

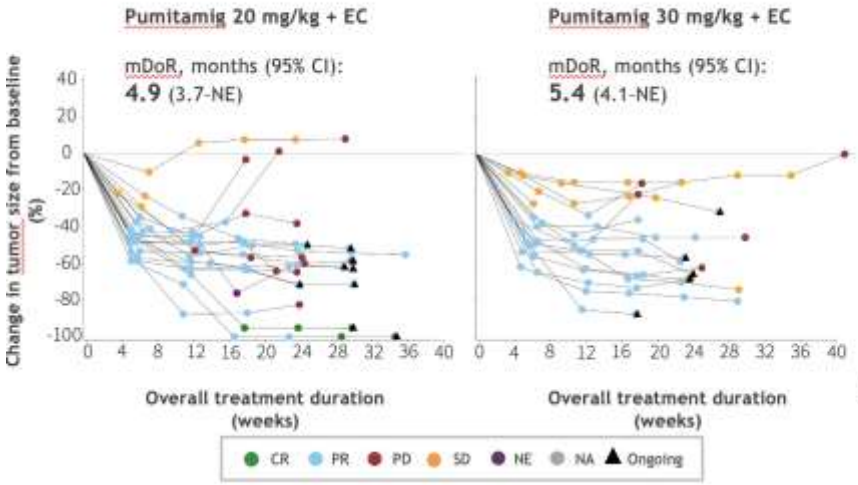
New strategies-challenging the first line setting-pumitamig

Global Phase 2 open-label, parallel group study to evaluate safety and preliminary efficacy of pumitamig + chemotherapy in patients with untreated ES-SCLC and previously treated SCLC (BNT327-01; NCT06449209)

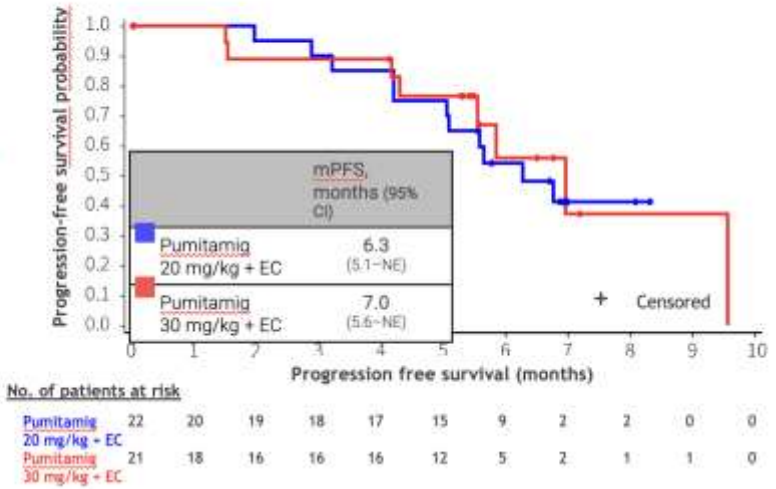




- **mDoR** in months (95% CI): **4.9** (4.2-NE) overall.



- **mPFS** in months (95% CI): **6.8** (5.6-NE) overall.



Ongoing ROSETTA Lung-01 Phase 3 trial…

Heymach et al. WCLC 2025

Antibody-drug conjugates

Target antigen

B7-H3

YL201[1,2]
Payload: Camptothecin derivative (YL0010014) (topoisomerase I inhibitor)

7MW3711[3,4]
Payload: Mtoxin™/MF6 (topoisomerase I inhibitor)

MHB088C[5]
Payload: SuperTopoi™ (topoisomerase I inhibitor)

B7-H3

I-DXd[6]
Payload: Deruxtecan (Topoisomerase I inhibitor)

HS-20093[7]
Payload: HS-9265 (Topoisomerase I inhibitor)

DLL3

Zocilurtatug pelitecan (ZL-1310)[8]
Payload: Camptothecin derivative (topoisomerase I inhibitor)

SEZ6

ABBV-706[9]
Payload: Topoisomerase I inhibitor

EGFR/HER3

Izalontamab brengitecan (BL-B01D1)[10]
Payload: Ed-04 (topoisomerase I inhibitor)

TROP2

Sacituzumab govitecan (SG)[11]
Payload: SN-38 (topoisomerase I inhibitor)

ADC, antibody-drug conjugate; B7-H3, B7 homolog 3; DLL3, delta-like ligand 3; EGFR, epidermal growth factor receptor; ES-SCLC, extensive-stage small cell lung cancer; HER3, human epidermal growth factor receptor 3; SEZ6, seizure related 6 homolog; TROP2, trophoblast cell surface antigen 2.

1. Ma Y, et al. Nat Med. 2025;31:1949–1957; 2. Medilink Therapeutics. Project Overview: YL201. Available at: https://www.medilinkthera.com/pipeline-details/3 (Accessed October 2025); 3. Li Z, et al. Presented at ASCO 2025. May 30–June 3. Chicago, US. Abstract 3036; 4. ADC Review. 7MW3711. Available at: https://www.adcreview.com/drugmap/7mw3711/ (Accessed October 2025); 5. Zhou C, et al. Presented at ASCO 2025. May 30–June 3. Chicago, US. Abstract 8510; 6. Owonikoko TK, et al. Presented at ASCO 2024. May 29–June 2. Chicago, US. Abstract TPS8126; 7. Xie L, et al. Presented at FACTOR 2024. June 20–22. Cleveland, US; 8. Patel MR, et al. Presented at ASCO 2025. May 30–June 3. Chicago, US. Abstract 3041; 9. Chandana SR, et al. Presented at ASCO 2024. May 31–June 4. Chicago, US. Abstract 3001; 10. Wan W, et al. Presented at AACR 2023. April 14–19; Orlando, FL. Poster #2642; 11. Gilead Sciences, Inc. Sacituzumab govitecan FDA PI, March 2025. Available at: https://www.gilead.com/-/media/files/pdfs/medicines/oncology/trodelvy/trodelvy_pi.pdf (Accessed October 2025); 12. NCT06498479. Available at: https://clinicaltrials.gov/study/NCT06498479 (Accessed October 2025); 13. Hayashi H, et al. Presented at JSMO 2025. March 6–8. Kobe, Japan; 14. NCT06500026. Available at: https://clinicaltrials.gov/study/NCT06500026 (Accessed October 2025); 15. Dowlati A, et al. *J Thorac Oncol*. 2025;20(6):799–808.

Cedida por Pedro Rocha

Ifinatamab-deruxtecan-IDeate-Lung01-relapsed disease

Dose-optimization (Part 1) and extension (Part 2) populations[1]

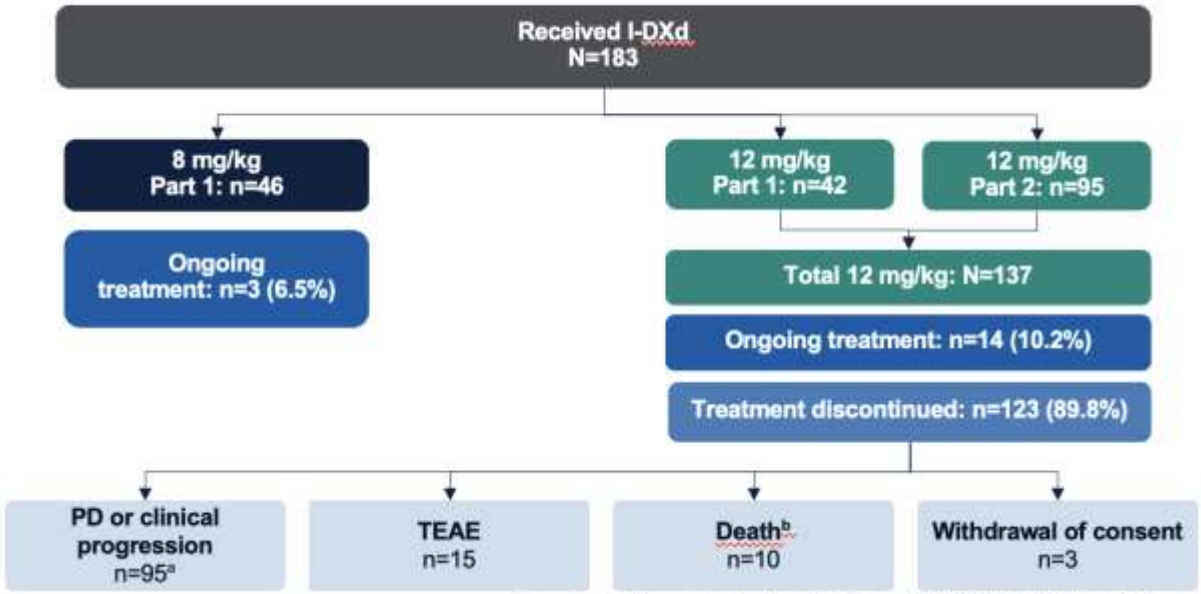


Figure adapted with permission from Ahn M-J, et al. Presented at WCLC 2025. Abstract OA06.03.

Total I-DXd 12 mg/kg population

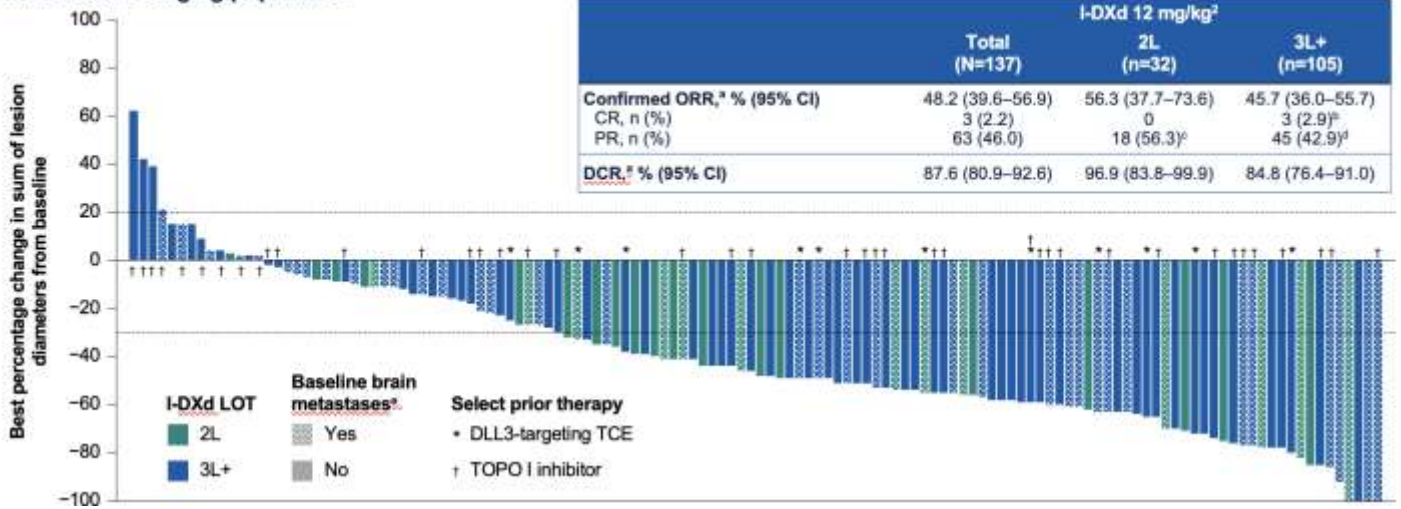
	Total I-DXd 12 mg/kg N=137
Median age (range), years	63 (34–79)
Male, n (%)	90 (65.7)
Race, n (%)	
Asian	67 (48.9)
White	63 (46.0)
Other or multiple	7 (5.1)
Region, n (%)	
Asia	66 (48.2)
Europe	40 (29.2)
North America	31 (22.6)
ECOG PS 1, n (%)	106 (77.4)
ES-SCLC at diagnosis, n (%)	111 (81.0)
Patients with brain/liver metastasis at baseline,[a] n (%)	52 (38.0) / 55 (40.1)

	Total I-DXd 12 mg/kg N=137
Number of prior lines of systemic therapy, n (%)	
1	32 (23.4)
2	75 (54.7)
3	30 (21.9)
Chemotherapy-free interval,[b] n (%)	
≤30 days	18 (13.1)
>30 to <90 days	40 (29.2)
≥90 days	72 (52.6)
Select anticancer therapy received, n (%)	
TOPO I inhibitor	44 (32.1)
Lurbinectedin	29 (21.2)
Amrubicin	12 (8.8)
DLL3-targeting TCE[c]	11 (8.0)
Prior anti–PD-(L)1 therapy received, n (%)	111 (81.0)

Rudin et al. JCO 2025

Ifinatamab-deruxtecan-IDeate-Lung01

Total I-DXd 12 mg/kg population[1]

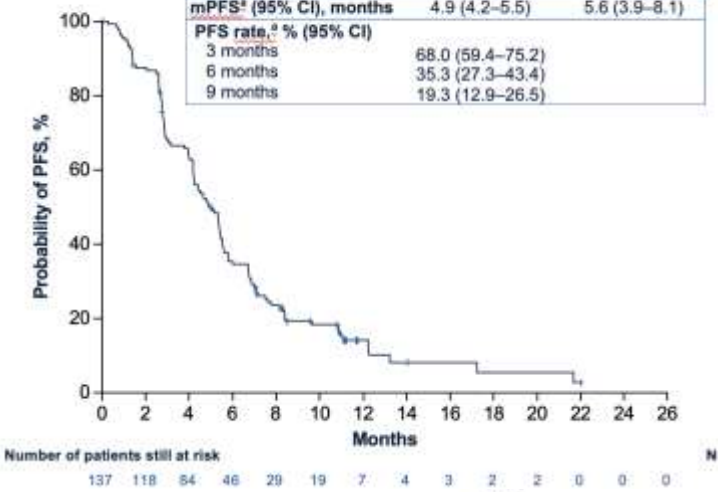


	I-DXd 12 mg/kg[2]		
	Total (N=137)	2L (n=32)	3L+ (n=105)
Confirmed ORR,[a] % (95% CI)	48.2 (39.6–56.9)	56.3 (37.7–73.6)	45.7 (36.0–55.7)
CR, n (%)	3 (2.2)	0	3 (2.9)[b]
PR, n (%)	63 (46.0)	18 (56.3)[c]	45 (42.9)[d]
DCR,[a] % (95% CI)	87.6 (80.9–92.6)	96.9 (83.8–99.9)	84.8 (76.4–91.0)

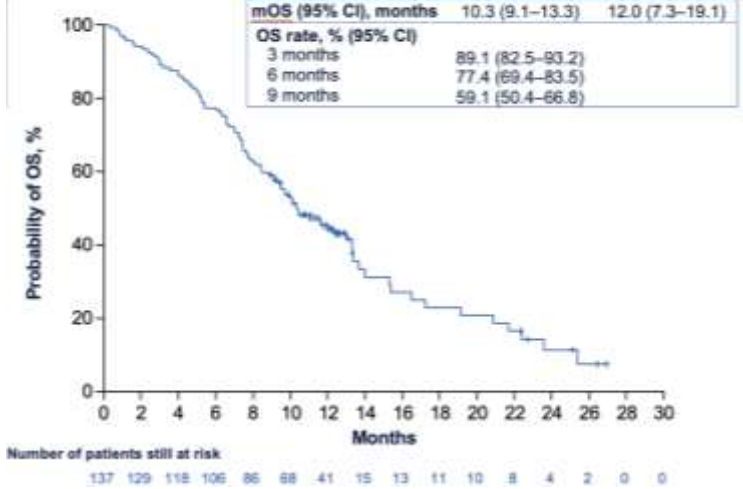
	I-DXd 12 mg/kg[2]	
	Total (N=137; Confirmed CR/PR: n=66)	2L (n=32)
Median TTR,[a,b] (range), months	1.4 (1.0–8.1)	1.4 (1.2–4.0)
Median DOR,[a,b] (95% CI), months	5.3 (4.0–6.5)	7.2 (3.6–NE)

PFS[1]

	I-DXd 12 mg/kg	
	Total (N=137)[2]	2L (n=32)[3]
mPFS[a] (95% CI), months	4.9 (4.2–5.5)	5.6 (3.9–8.1)
PFS rate,[a] % (95% CI)		
3 months	68.0 (59.4–75.2)	
6 months	35.3 (27.3–43.4)	
9 months	19.3 (12.9–26.5)	



	I-DXd 12 mg/kg	
	Total (N=137)[2]	2L (n=32)[3]
mOS (95% CI), months	10.3 (9.1–13.3)	12.0 (7.3–19.1)
OS rate, % (95% CI)		
3 months	89.1 (82.5–93.2)	
6 months	77.4 (69.4–83.5)	
9 months	59.1 (50.4–66.8)	

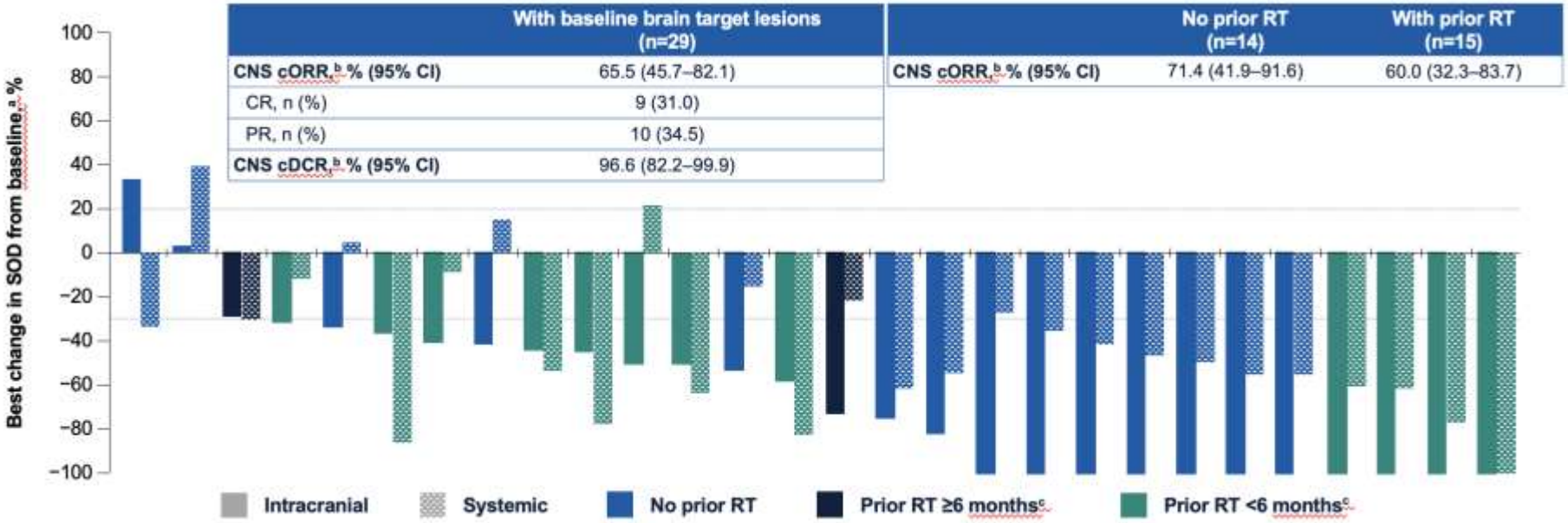


Rudin et al. JCO 2025

Ifinatamab-deruxtecan-IDeate-Lung01-intracraneal activity

Intracranial cORR in patients with or without prior RT to the brain for baseline brain metastases

	cORR,[a] % (95% CI)
With baseline brain metastases (n=65)	46.2 (33.7–59.0)
No prior RT (n=26)	57.7 (36.9–76.6)
Prior RT (n=39)	38.5 (23.4–55.4)
<6 months before study[b] (n=28)	39.3 (21.5–59.4)
≥6 months before study[b] (n=11)	36.4 (10.9–69.2)



	With baseline brain target lesions (n=29)
CNS cORR,[b] % (95% CI)	65.5 (45.7–82.1)
CR, n (%)	9 (31.0)
PR, n (%)	10 (34.5)
CNS cDCR,[b] % (95% CI)	96.6 (82.2–99.9)

	No prior RT (n=14)	With prior RT (n=15)
CNS cORR,[b] % (95% CI)	71.4 (41.9–91.6)	60.0 (32.3–83.7)

Rocha et al. ESMO 2025

ADCs in pretreated SCLC

	ABBV-706 1.8mg/kg (N=41)	QLC5508 (MHB088C) 1.6-2.4mg/kg (N=103)	I-DXd 12mg/kg (N=137)	HS20093 (GSK5764227) 8mg/kg (N=31)[1]	YL201 1.6-2.8mg/kg (N=72)[2]	Sacituzumab Govitecan (N=43)[3]
Target	SEZ6	B7-H3	B7-H3	B7-H3	B7-H3	TROP2
Payload	Top1 inhibitor	Top1 inhibitor (SuperTopoi™)	Top1 inhibitor (DXd)	Top1 inhibitor (HS-9265)	Top1 inhibitor	Top1 inhibitor (SN-38)
DAR	6	4	4	4	8	7.6
Linker	Cleavable	Cleavable	Cleavable	Cleavable	Cleavable	Cleavable
ORR/DCR	56%	36.9/90.3%	48.2/87.6%	61.3/80.6%	63.9/91.7%	41.9/83.7%
mPFS/OS	6.8 months/ 60%(9month OS)	5.72/11.50 months	4.9/10.3 months	5.9/9.8 months	6.3/- months	4.4/13.6 months
Main AEs	Hematological toxicity	Hematological toxicity	Hematological toxicity/GI toxicity	Hematological toxicity	Hematological toxicity	Diarrhea/Hematological toxicity

1) WCLC 2024, 2) Ma Y, et al. Nat Med. 2025 Jun;31(6):1949-1957. 3) Dowlati A et al. J Thorac Oncol. 2025 Jun;20(6):799-808.

Yoshida WCLC 2025

Prospective observation study in Japan (J-TAIL2) 58% of pts did NOT meet the eligibility criteria in IMpower133

Key Takeaways

Elderly	17% Poor PS	Brain metastasis	7% ILD/ILA	Auto immune
Similar Efficacy/irAE PS and G8 as key indicators Higher AEs	PS2: similar efficacy Higher AEs	CNS efficacy(+) 70% CNS progression →Close monitoring + Local control	Mild ILD/ILA ICI acceptable monitoring for ILD	Steroid<10mg And Stable: ICI acceptable Neurologic PNS: not recommended

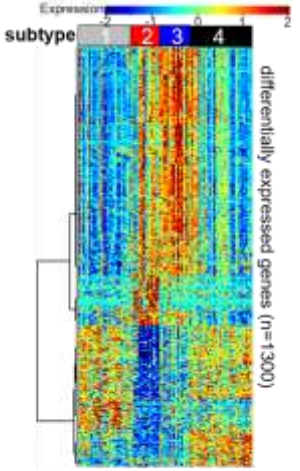
Dose adjustment is key!

Real-world evidence shows "one size does not fit all".

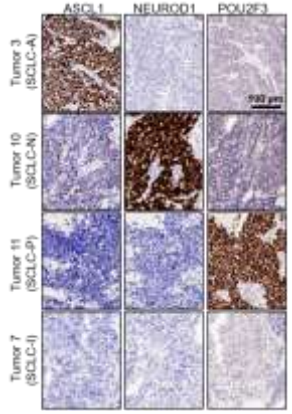
Modified from Tachihara M, WCLC 2025

Translational research

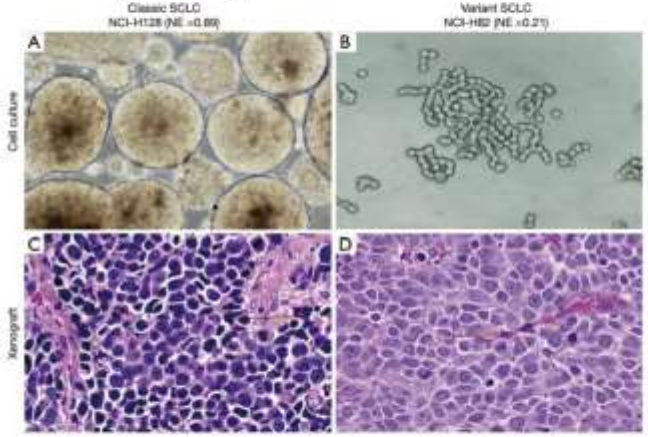
SCLC is a heterogeneous disease



SCLC tumors (n=81)
George et al.

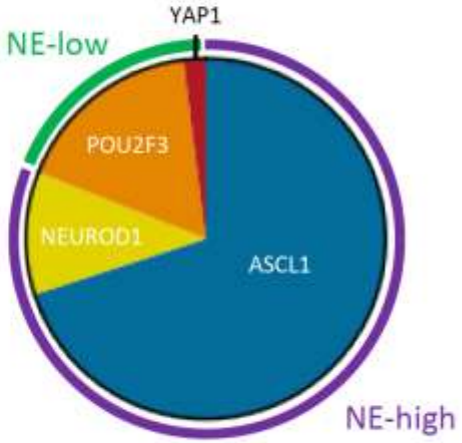


"Classic" and "variant" phenotypes are described[1,2]

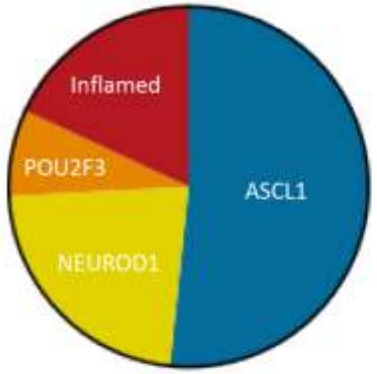


Zhang et al. *Translational Lung Cancer Research* 2018

SCLC can be divided into four molecular subtypes[3]



A novel inflamed SCLC subtype is identified[4]



IHC and molecular profiling fails to confirm a YAP1-defined subtype[5,6]

[1]Carney et al. *Cancer Research* 1985
[2]Gazdar et al. *Cancer Research* 1985
[3]Rudin et al. *Nature Reviews Cancer* 2019
[4]Gay et al. *Cancer Cell* 2021
[5]Baine et al. *Journal of Thoracic Oncology* 2021
[6]Ng et al. *Clinical Cancer Research* 2024
modified from Megyesfalvi et al. *A Cancer Journal for Clinicians* 2023

Biomarker driven strategies in maintenance

S2409-PRISM: A Multicohort **PR**ec**I**sion **S**CLC Subtype **M**aintenance Phase II Trial of Durvalumab Versus Biomarker-Directed Novel Agents in Combination with Durvalumab in Extensive Stage Small Cell Lung Cancer (ES-SCLC)

Step 1: Tissue screening & Induction (n=838)

- **ES-SCLC Screening**
- **Tissue available for tes**
- **As**
  St
  Le
- **Allows consent after initial cycle for tissue screening**
- **Receipt of at least 4 cycles of durvalumab during induction**

Step 2: Randomization (n=312)

Subtypes A/N, SLFN11 pos → **Durvalumab + AZD5305** — PARP inhibitor

Will these studies be meaningful in the new 1L or maintenance scenarios?

Subtypes A/N, SLFN11 neg
N=84 (76 eligible)
→ **Durvalumab + ceralasertib** — ATR1 inhibitor
→ **Durvalumab**

Subtype I
N=84 (76 eligible)
→ **Durvalumab + monalizumab** — NKG2A inhibitor
→ **Durvalumab**

Primary Endpoints: PFS

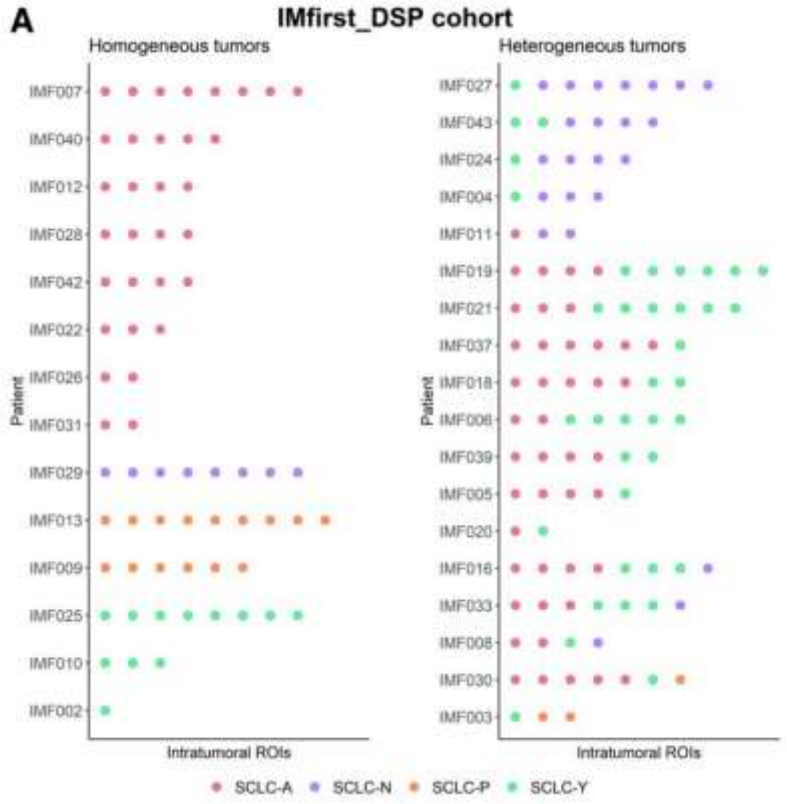
Secondary Endpoints: OS, Frequency, Severity of Adverse Events
Safety Run-in for Durva + AZD5305

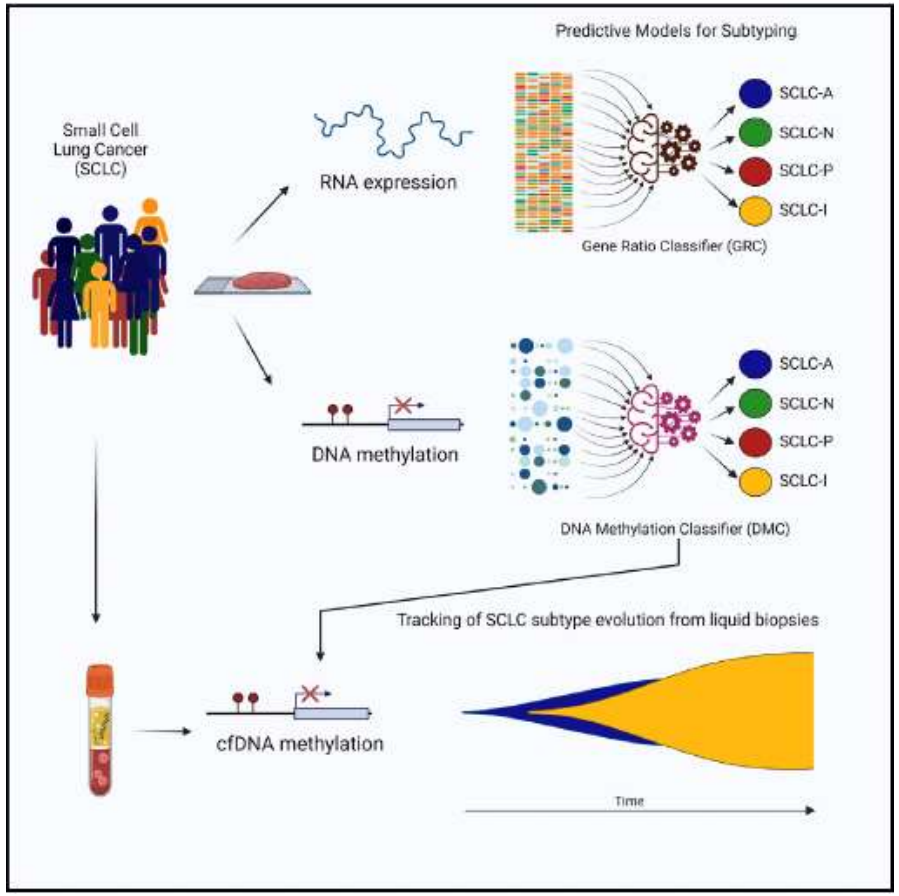
SWOG CANCER RESEARCH NETWORK

NCI National Clinical Trials Network — a National Cancer Institute program

NCI Community Oncology Research Program

SCLC is heterogeneous at diagnosis and changes over treatment

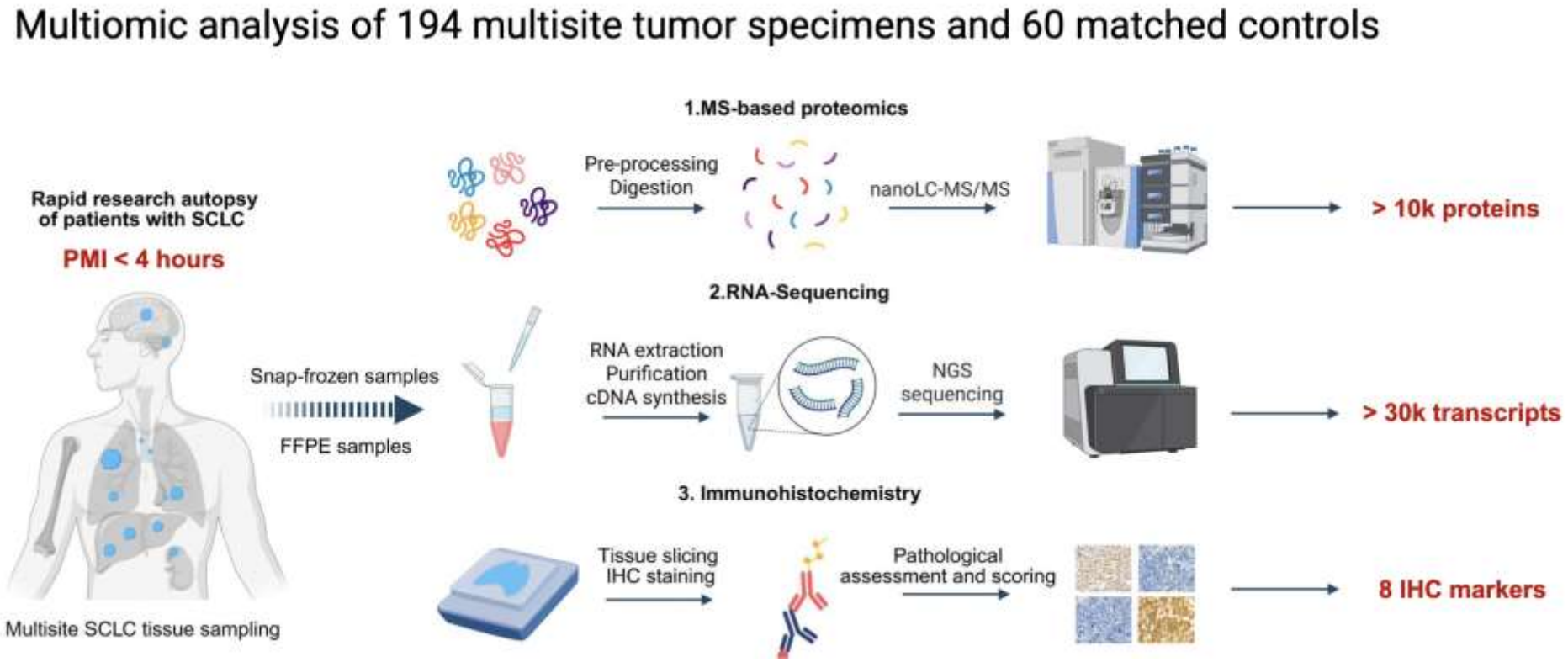




Peressini et al. 2024; Heeke et al. Cancer Cell 2024

Current initiatives

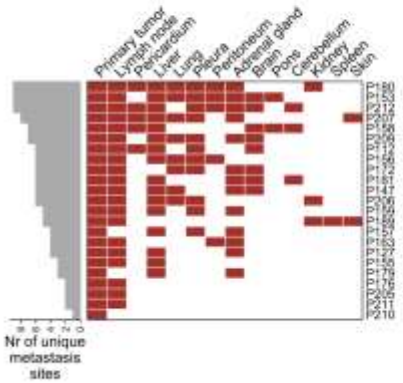
Spanish collaborative network

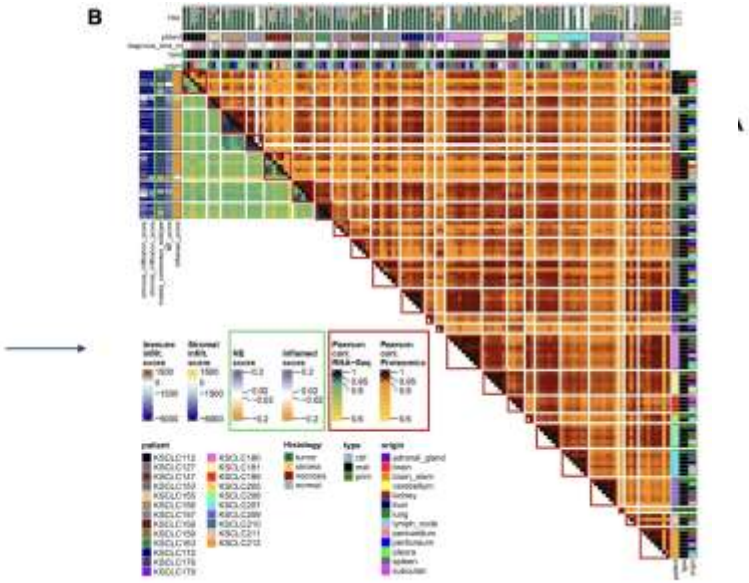


Megyesfalvi et al. WCLC 2025

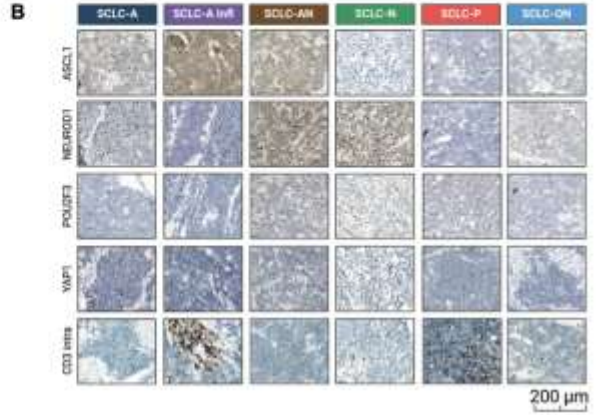
High intra and interlesion heterogeneity in relevant targets

Overview of Inter-Lesion Tumor Heterogeneity in SCLC

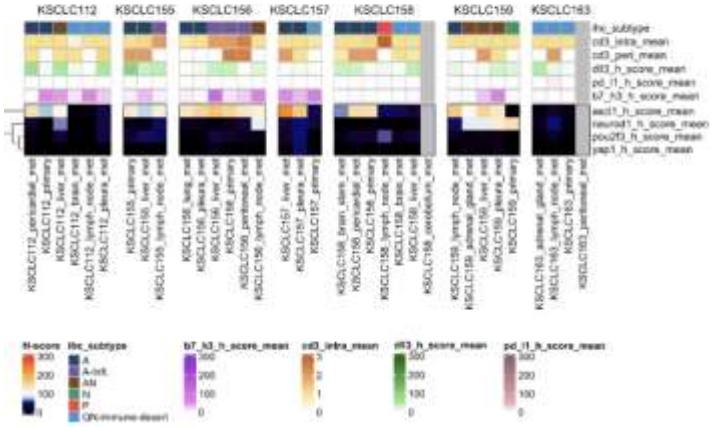




SCLC molecular subtypes and therapeutic targets show high intra-tumoral and inter-lesion heterogeneity as revealed by IHC



Overall inter-lesion molecular subtype heterogeneity (IHC)



Take-home messages

Several known clinically relevant proteins and therapeutic targets have heterogeneous expression profiles across tumor sites within a patient with SCLC.

Molecular subtypes show both intra-tumoral and inter-site variability.

The identified stably expressed molecular targets could lead to more effective treatments in SCLC.

Megyesfalvi et al. WCLC 2025

Conclusions

- Unprecedented opportunities for SCLC patients, but not all patients represented in trials
- Multiple new strategies show efficacy in SCLC, early data, phase III trials ongoing
- Toxicities need to be known and managed appropiately
- Combining to the SoC might result in overtreating patients
- Still no biomakers in place to select the best strategy for each patient-rational sequencing is required
- More research is needed to address the heterogeneity and plasticity of SCLC

16th CONGRESS Lung ON CANCER

BARCELONA 27 / 28 NOVEMBER 2025

THANK YOU

GECP lung cancer research