Lung Cancer UPDATES
ESMO HIGHLIGHTS
17 - 21 OCTUBRE 2025
Berlin, Germany

GECP lung cancer research

Carcinoma de pulmón microcítico II

Manuel Dómine
Fundación Jiménez Díaz Campus Hospitalario IIS-FJD
Universidad Autónoma de Madrid

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Pacientes pretratados

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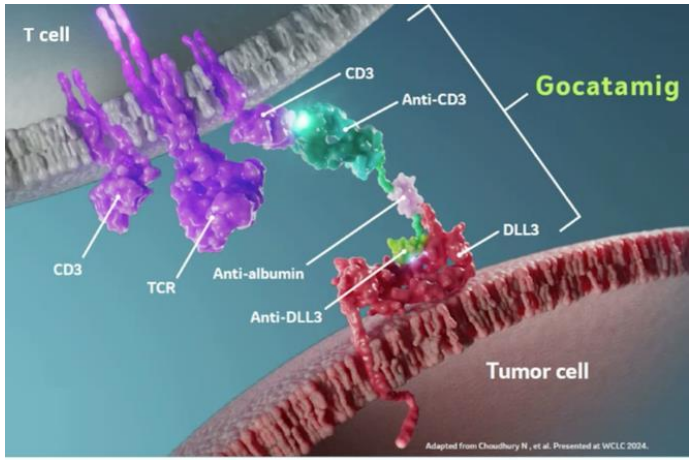
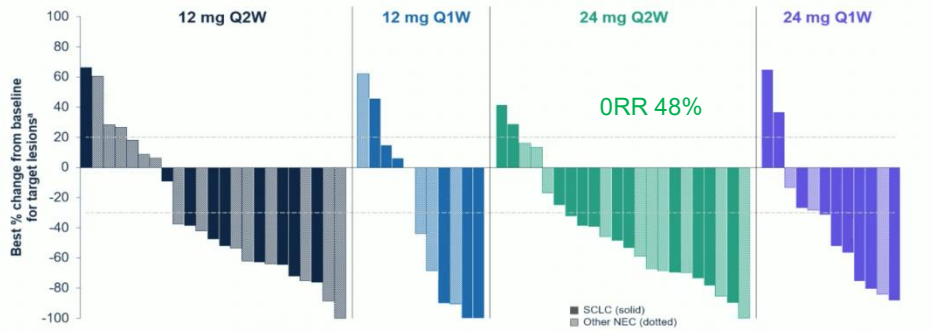
Phase 1/2 Gocatamig monotherapy in SCLC and other NEC

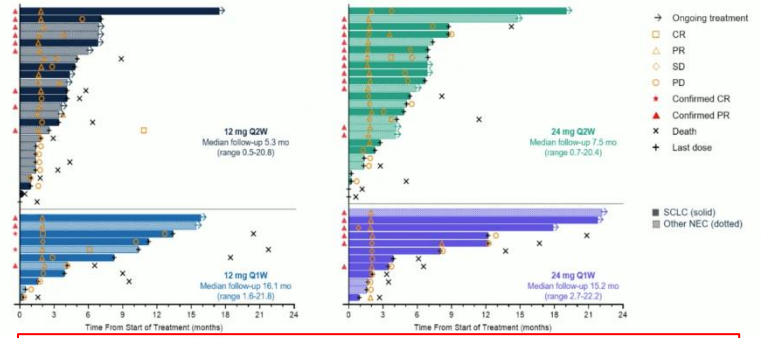


Gocatamig Antitumor Activity



[a]Among 68 participants who received any amount of study treatment and had at least one postbaseline scan.
Data cutoff date 28 February 2025.

Duration of Treatment and Response[a]



Median DOR was 10.8 months (range 1.8-19.8 months) with 17/32 (53%) of responses ongoing at data cutoff

[a]Based on investigator assessment per RECIST v1.1. Imaging was scheduled Q8W. Shown are the assessments at which the first CR, PR, SD, or PD occurred.
Data cutoff date 28 February 2025.

Phase 1/2 6070-001 Gocatamig Monotherapy in SCLC and Other NEC

Key eligibility criteria

- Age ≥18 years
- SCLC relapsed/refractory to ≥1 prior line of platinum-based chemotherapy OR
- Other DLL3-expressing NEC relapsed/refractory to standard therapy (or standard therapy does not exist or is considered inappropriate)
- ECOG PS 0 or 1

Gocatamig monotherapy dosing

- 12 mg or 24 mg IV Q1W or Q2W with step-up dosing[a]

Key study objectives

- Safety and tolerability: AEs, DLTs
- Preliminary antitumor activity: ORR assessed by investigator per RECIST v1.1

Participants with SCLC or other NEC treated in a 12-mg or 24-mg Q1W or Q2W target dose cohort (N=73)[b]

- 12 mg Q2W (n=25)
- 12 mg Q1W (n=11)
- 24 mg Q2W (n=25)
- 24 mg Q1W (n=12)

[a]The target dose of 12 mg was administered Q1W or Q2W following a single priming dose of 1 mg. The target dose of 24 mg was administered Q1W or Q2W following sequential single priming doses of 1 mg and 12 mg.
[b]Includes 39 participants with SCLC, 29 with neuroendocrine carcinomas, and 5 high-grade neuroendocrine tumors; excludes participants with neuroendocrine prostate cancer.
https://clinicaltrials.gov/. NCT04471727

Summary of Treatment-Related Adverse Events

	12 mg Q2W (n=25)	12 mg Q1W (n=11)	24 mg Q2W (n=25)	24 mg Q1W (n=12)	All Cohorts (N=73)
TRAEs, n (%)	23 (92)	11 (100)	24 (96)	11 (92)	69 (95)
Grade 3-5	6 (24)	1 (9)	8 (32)	6 (50)	21 (29)
Serious	2 (8)	3 (27)	4 (16)	4 (33)	13 (18)
Led to treatment discontinuation	0	0	1 (4)	1 (8)	2 (3)
Led to death	0	0	0	1[a] (8)	1[a] (1)

TRAEs of interest by highest grade, n (%)	All Cohorts (N=73)
CRS, any grade	40[b] (55)
Grade 1	24 (33)
Grade 2	15 (21)
Grade 4	1 (1)
ICANS, any grade	5 (7)
Grade 1	3 (4)
Grade 2	2 (3)

TRAEs with incidence ≥20%, n (%)	All Cohorts (N=73)	
	Any grade	Grade 3-5
CRS	40 (55)	1 (1)
Fatigue	38 (52)	2 (3)
Dysgeusia	33 (45)	0 (0)
Nausea	29 (40)	0 (0)
Diarrhea	23 (32)	3 (4)
Vomiting	23 (32)	0 (0)
Decreased appetite	21 (29)	1 (1)
Weight decreased	17 (23)	2 (3)

[a]One participant died from treatment-related pneumonitis. [b]90% of CRS events occurred on C1D1 or C1D8.
All AEs were graded per CTCAE v5.0 except for CRS and ICANS, which were graded per ASTCT 2019 criteria.
Data cutoff date 28 February 2025.

CONCLUSIONES

Gocatamib otro biespecíficos DLL3- CD3 en CPM y otros NEC

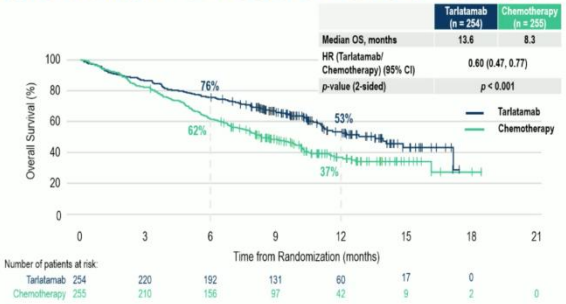
- eficaz con RR 44%, DOR 10.8 meses,
- toxicidad manejable 98% CRS grado 1-2

Pacientes pretratados

Detailed safety analysis of phase III study DeLLphi-304: tarlatamab vs chemotherapy for previously treated SCLC

Tarlatamab Improved Overall Survival in Second-line SCLC Treatment

- In the phase 3 DeLLphi-304 study, tarlatamab significantly improved overall survival and progression-free survival, reducing the risk of death by 40% compared to chemotherapy, and showed a manageable safety profile[1]



Here, we present data from an additional detailed safety analysis that further characterized adverse events from the DeLLphi-304 study.

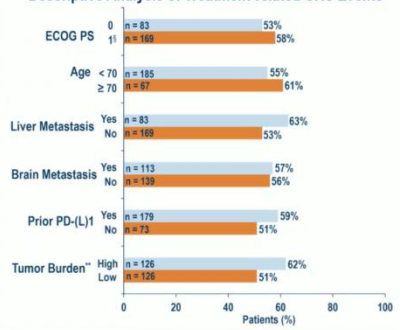
CI, confidence interval; HR, hazard ratio; OS, overall survival; SCLC, small cell lung cancer;
1. Mountzios G, et al. *N Engl J Med*. 2025;393:349-361.

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.

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

*TRAEs meeting an overall ≥ 20% incidence in either arm.
CRS, cytokine release syndrome; **mo**, months; **TRAE**, treatment-related adverse event.

Incidence of ICANS and Dysgeusia with Tarlatamab

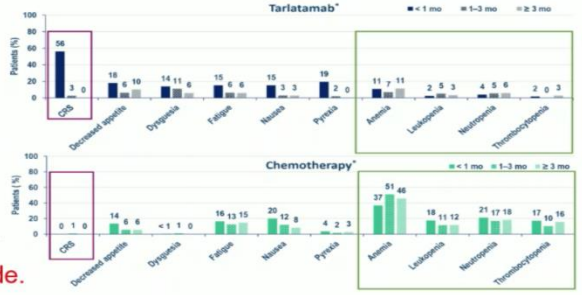
Treatment-related ICANS	Tarlatamab (N = 252)
Patients with events*, n'/N (%)	15/252 (6)
ICANS severity†, n/n' (%)	
Grade 1	7/15 (47)
Grade 2	7/15 (47)
Grade ≥ 3‡	1/15 (7)
Leading to discontinuation	1/15 (7)
Patients with resolved events†, n/n' (%)	14/15 (93)
Median duration among resolved cases, days (IQR)	4 (2—7)
Median time to resolution, days (95% CI)	4 (2, 7)
Occurrence of both ICANS and CRS events §, n/n' (%)	14/15 (93)

Treatment-related Dysgeusia	Tarlatamab (N = 252)
Patients with events*, n'/N (%)	58/252 (23)
Dysgeusia severity†, n/n' (%)	
Grade 1	43/58 (74)
Grade 2	15/58 (26)
Leading to discontinuation	0
Patients with resolved events†, n/n' (%)	17/58 (29)
Median time to onset, days (IQR)	28 (15—42)
Median duration among resolved cases, days (IQR)	126 (17—143)

- ICANS events were infrequent with tarlatamab treatment, generally grade 1 or 2, and the most commonly associated symptoms were depressed level of consciousness (5/15), confusion (5/15), and dysgraphia (4/15)
- Dysgeusia was the most common neurologic TRAE** with tarlatamab and was predominantly grade 1; there were no tarlatamab treatment discontinuations due to dysgeusia

*Number of patients with events of ICANS or dysgeusia were based on number of patients in the safety analysis set [N]. †Incidence of ICANS and dysgeusia were calculated using the number of patients reporting ICANS or dysgeusia, (n'), as denominator, respectively. ‡Grade 4 ICANS events were not observed. A single grade 5 treatment-related adverse event observed with tarlatamab was attributed to ICANS in the setting of progressive neurological decline concurrent with persistent fever, hypoxemia, and hypotension. §Occurrence of both ICANS and CRS was calculated using the number of patients reporting ICANS, (n'), as denominator. **45% of patients receiving tarlatamab reported neurologic TRAEs of any grade. Dysgeusia was categorized under neurological disorders based on MedDRA coding classification.
CI, confidence interval; **CRS**, cytokine release syndrome; **ICANS**, immune effector cell-associated neurotoxicity syndrome; **IQR**, interquartile range; **MedDRA**, Medical Dictionary for Regulatory Activities; **TRAE**, treatment-related adverse event.

What do these updated data add?



- ✓Tarlatamab, as a first-in-class DLL3 BiTE, introduced new toxicities for solid tumour oncologists- *this is a true learning curve…*
- ✓**45%** of pts on Tarlatamab reported a neurologic TRAE of any grade.
- ✓**CRS** occurred mainly in cycle 1 (~56%), almost all low-grade (G1–2); incidence decreased markedly thereafter.
- ✓**ICANS** events remained rare (6%), confirming a very low neurotoxicity risk.
- ✓**Neutropenia** ~4–6% (Grade ≥3 ≈2–3%), notably lower versus chemotherapy.
- ✓**Dysgeusia** (~11–14%), mild and reversible- affects QoL more than safety; counselling is key.

Helena Linardou, MD PhD, Athens, Greece

Schuler M, et al. WCLC 2025

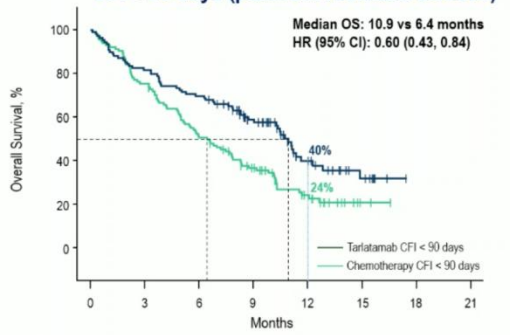
Pacientes pretratados

Phase III study DeLLphi-304: Tarlatamab as second-linev treatment for SCLC: Outcomes by chemotherapy-free interval (CFI) and prior PD-L1 inhibitor

Overall Survival by Chemotherapy-free Interval

DeLLphi 304

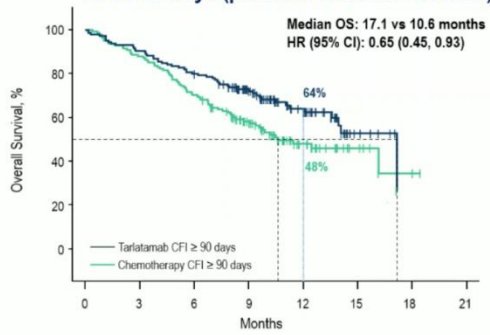
CFI < 90 days (platinum-resistant disease)



Number of Patients at Risk:

Tarlatamab CFI < 90 days	109	89	76	50	21	9	0
Chemotherapy CFI < 90 days	114	86	57	36	16	2	0

CFI ≥ 90 days (platinum-sensitive disease)



Number of Patients at Risk:

Tarlatamab CFI ≥ 90 days	145	131	116	81	39	8	0
Chemotherapy CFI ≥ 90 days	141	124	99	61	26	7	2

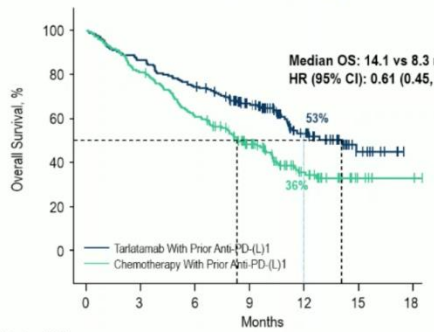
- Tarlatamab reduced the risk of death by 40% in the overall study population and this OS benefit extended to patients with platinum-resistant SCLC (OS HR = 0.60).
- Among patients whose disease advanced within 14 days of last platinum-based treatment,* the 6-month KM estimate for OS was 55% with tarlatamab vs 35% with chemotherapy.

*n = 20 in both the tarlatamab and chemotherapy groups.
CFI, chemotherapy-free interval; **CI**, confidence interval; **HR**, hazard ratio; **KM**, Kaplan-Meier; **OS**, overall survival; **SCLC**, small cell lung cancer.

Overall Survival by Prior Anti-PD-(L)1 Status

DeLLphi 304

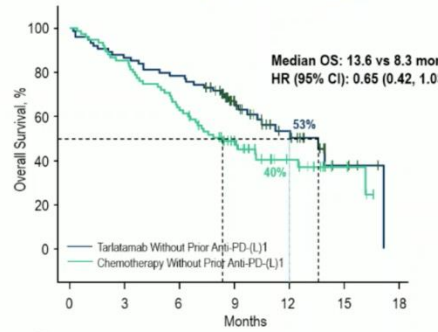
Prior Anti-PD-(L)1



Number of Patients at Risk:

Tarlatamab With Prior Anti-PD-(L)1	180	156	134	96	43	13	0
Chemotherapy With Prior Anti-PD-(L)1	180	146	109	70	30	5	2

No prior Anti-PD-(L)1



Number of Patients at Risk:

Tarlatamab Without Prior Anti-PD-(L)1	74	64	58	35	17	4	0
Chemotherapy Without Prior Anti-PD-(L)1	75	64	47	27	12	4	0

- Prior anti-PD-(L)1 exposure did not impact survival benefit of tarlatamab over chemotherapy.

CI, confidence interval; **HR**, hazard ratio; **OS**, overall survival; **PD-(L)1**, programmed death (ligand)-1.

Tarlatamab Outcomes by PD-L1 and CFI

Conclusions

- Tarlatamab is THE 2nd line standard of care with better PFS, better OS, less toxicity, better symptom improvement.
- Prior PD-L1 exposure did not impact positive result in favor of tarlatamab
- Prior chemotherapy-free interval did not impact positive result in favor of tarlatamab
- Interestingly, this study demonstrates better overall survival in the group with chemotherapy-free interval ≥90 days, which may reflect disease control with later lines of cytotoxic regimens.
- CRS rates are not substantially different between subgroups.
  - No reliable way of prospectively identifying those that develop CRS prior to treatment

Jacob Sands, MD

I-DXd demonstrated promising systemic and intracranial efficacy in patients with baseline BM

	With baseline BM (n=65)		Without baseline BM (n=72)
	Intracranial	Systemic	Systemic
cORR,[a] % (95% CI)	46.2% (33.7–59.0)	46.2% (33.7–59.0)	50.0% (38.0–62.0)
cBOR,[a] n (%)			
CR	20 (30.8%)	1 (1.5%)	2 (2.8%)
PR	10 (15.4%)	29 (44.6%)	34 (47.2%)
SD	29 (44.6%)	28 (43.1%)	26 (36.1%)
PD	1 (1.5%)	5 (7.7%)	5 (6.9%)
NE	5 (7.7%)[b]	2 (3.1%)[c]	5 (6.9%)[d]
cDCR,[a] % (95% CI)	90.8% (81.0–96.5)	89.2% (79.1–95.6)	86.1% (75.9–93.1)
DOR,[a] median (95% CI), months	6.2 (4.0–7.9)	4.3 (3.0–5.8)	5.9 (4.0–8.3)
TTR,[a] median (range), months	1.4 (0.9–8.5)	1.4 (1.0–8.1)	1.4 (1.2–4.0)
PFS,[a] median (95% CI), months	—	4.5 (4.0–5.4)	5.4 (4.2–6.7)
OS, median (95% CI), months	—	10.4 (7.9–15.3)	10.1 (8.4–13.3)

- **Concordance** between systemic and CNS **objective response: 75.4%**
- **Concordance** between systemic and CNS **disease control: 86.2%**

- OS and PFS were similar for patients with and without baseline BM

Data cutoff: March 3, 2025.
[a]By CNS BICR using a version of RECIST 1.1 modified for assessment of CNS tumors for intracranial response and by BICR per RECIST 1.1 for systemic response. [b]Reason for NE was no adequate post-baseline assessment (n=5). [c]Reason for NE was no adequate post-baseline assessment (n=2). [d]Reason for NE was no adequate post-baseline assessment (n=3) or SD too early (n=2).
BICR, blinded independent central review; BM, brain metastases; cBOR, confirmed best overall response; cDCR, confirmed disease control rate; CI, confidence interval; CNS, central nervous system; cORR, confirmed objective response rate; CR, complete response; DOR, duration of response; NE, not evaluable; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; SD, stable disease; TTR, time to response.

I-DXd demonstrated promising intracranial efficacy regardless of prior treatment for baseline BM

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

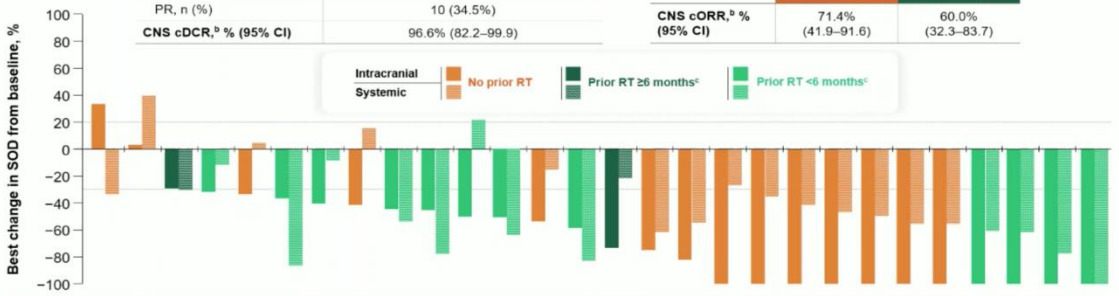
	cORR,[a] % (95% CI)
With baseline BM (n=65)	46.2% (33.7–59.0)
No prior RT (n=26)	57.7% (36.9–76.6)
Prior RT (n=39)	38.5% (23.4–55.4)
<6 months before study[b] (n=28)	39.3% (21.5–59.4)
≥6 months before study[b] (n=11)	36.4% (10.9–69.2)

Data cutoff: March 3, 2025.
[a]By CNS BICR using a version of RECIST 1.1 modified for assessment of CNS tumors. [b]Time from last RT of brain until first dose of study treatment.
BICR, blinded independent central review; BM, brain metastases; CI, confidence interval; CNS, central nervous system; cORR, confirmed objective response rate; RECIST 1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; RT, radiotherapy.

I-DXd demonstrated promising responses in patients with brain target lesions[a]

	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)



Concordance between systemic and CNS **objective response: 69.0%**

Data cutoff: March 3, 2025.
[a]Only patients with measurable disease at baseline and ≥1 post-baseline assessment are included in the plot (n=28); 1 patient was excluded due to a lack of post-baseline assessment. [b]By CNS BICR using a version of RECIST 1.1 modified for assessment of CNS tumors. [c]Time from last RT of brain until first dose of study treatment.
BICR, blinded independent central review; cDCR, confirmed disease control rate; CI, confidence interval; CNS, central nervous system; cORR, confirmed objective response rate; CR, complete response; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; RT, radiotherapy; SOD, sum of diameters.

Conclusions

- Intracranial efficacy with I-DXd 12 mg/kg was promising, with 30.8% of patients achieving an intracranial CR, contributing to an intracranial cORR of 46.2% and DCR of 90.8%
  - Intracranial cORR was 57.7% among 26 patients who had not received prior brain RT for baseline BM
  - In 29 patients with baseline brain target lesions, intracranial cORR was 65.5% (9 CR, 10 PR), and almost all patients experienced intracranial disease control (96.6%)
- In 72 patients without baseline BM, progression in the brain was uncommon (12.5%)
- The safety profile for patients with and without baseline BM was consistent with the overall I-DXd 12-mg/kg population[1]
- The intracranial activity of I-DXd will be investigated further in the ongoing Phase 3 IDeate-Lung02 study (NCT06203210), which is comparing I-DXd with treatment of physician's choice (topotecan, amrubicin, or lurbinectedin) in patients with relapsed SCLC[2]

Data cutoff: March 3, 2025.
BM, brain metastases; cORR, confirmed objective response rate; CR, confirmed response; DCR, disease control rate; PR, partial response; RT, radiotherapy; SCLC, small cell lung cancer.
1. Ahn M-J, et al. Oral presentation at IASLC 2025 World Conference on Lung Cancer. September 6–9, 2025; Barcelona, Spain. Presentation OA06.03. 2. Owonikoko TK, et al. Poster presented at the 2024 American Society of Clinical Oncology Annual Meeting. May 31–June 4, 2024; Chicago, IL, USA. Presentation TPS8126.

Carcinoma de pulmón Microcítico

CONCLUSIONES

- **1ª línea:**
  - Resultados muy prometedores de los estudio fase I con combinaciones de quimioterapia + anti-PD-L1 + biespecíficos DLL3- CD3 (Tarlatamab, obrixttamig): alta eficacia, toxicidad controlable.
- **Mantenimiento::**
  - **Tratamiento estándar**: IMforte (lurbinectedina + Atezolizumab tras 4 ciclos de quimioterapia + atezolizumab. Lurbi + atezo mostró menor proporción de nuevas lesiones hepáticas vs Atezo), en contraste lurbi+ atezo presentó una mayor proporción de metástasis cerebrales como progresión inici**al.**
  - **Ceralasertib** (inhibidor ATR): mantenimiento tras 4 ciclos de quimioterapia + atezolizumab es tolerable, no mejora los datos previos en PFS y RR, parece que puede mostrar una supervivencia mayor (estudio fase II con sólo 30 pacientes)
- **Pretratados**
  - **Tarlatamab (DeLLphi 304)** es el first-in-class DLL3 BITE, introdujo nueva toxicidades para tumores sólidos supone una curva de aprendizaje para oncólogos. Toxicidad detallada:La mayoría de los CRS (56%) ocurrieron en ciclo 1 y fueron G1-2, ICANS raros (6%), disgeusia11-14% (consejo por oncólogo). Expresión de PD-L1 ni el intervalo libre de quimioterapia no impacta en resultados positivo de tarlatamab
  - **Ifinatamab-deruxtecan (ADC) anti B7 H3** muestra una eficacia muy prometedora con un 30.8% de RC 46% de RG intracraneales, 57% en pacientes que no habían recibido RT para metástasis cerebrales
  - **Gocatamib** en CPM y otros NEC, otro biespecíficos DLL3- CD3, es eficaz con RR 44%, DOR 10.8 meses, toxicidad manejable 98% CRS grado 1-2
- **Conclusiones**