Lung Cancer UPDATES
ESMO HIGHLIGTHS
20-24 OCTUBRE 2023
Madrid, Spain

Iniciativa científica de:
GECP
lung cancer research

Carcinoma microcítico y otros tumores torácicos

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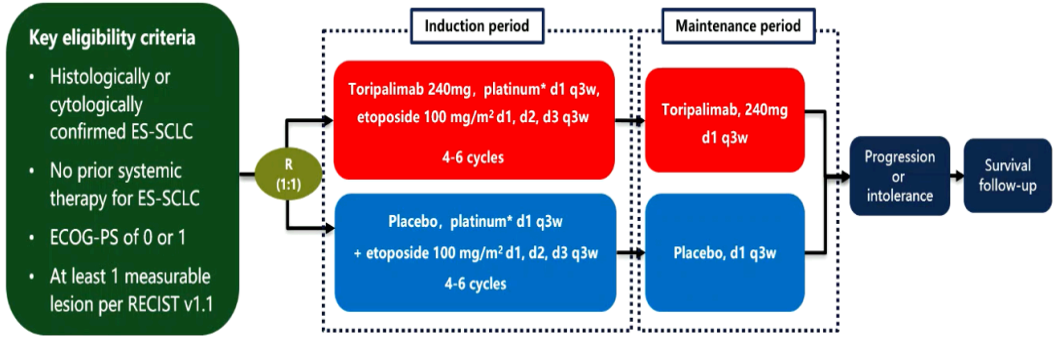
Hospital Universitario Fundación Jiménez Díaz. IIS-FJD

EXTENTORCH: Randomized phase III of toripalimab vs placebo in combination with chemotherapy as 1st line in EE-SCLC

Iniciativa científica de: GECP lung cancer research

Study Design



Stratification factors
- Gender
- ECOG PS score (0 vs. 1)

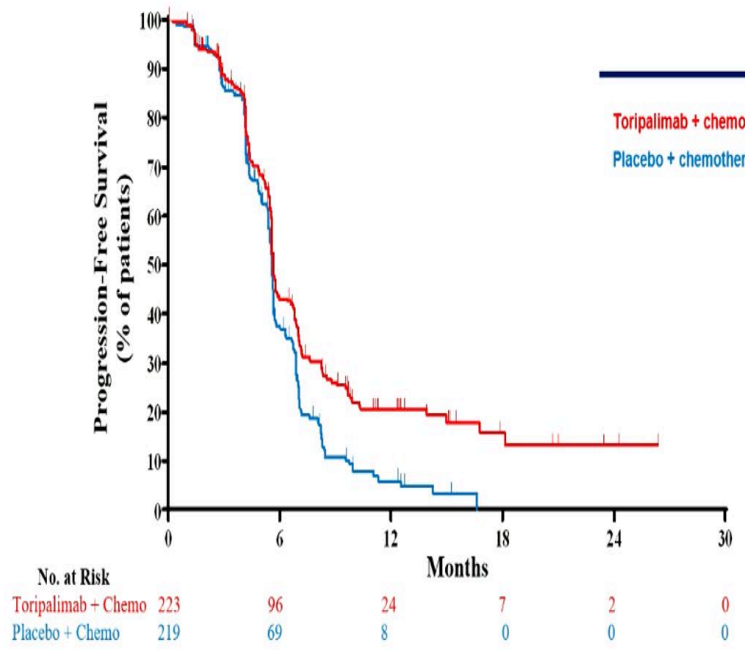
Primary endpoint: PFS by investigator per RECIST v1.1 and OS

Secondary endpoints: BICR-assessed PFS, ORR, DCR, DoR, TTR, safety

* Carboplatin: AUC 5 mg/mL/min IV, Day 1; Cisplatinum: 75mg/m² IV, Day1
Abbreviation: ES-SCLC, extensive stage small cell lung cancer; SCLC, small cell lung cancer; ECOG-PS, Eastern Cooperative Oncology Group performance status; RECIST, Response Evaluation Criteria in Solid Tumors; PFS, progression-free survival; OS, overall survival; BICR, Blind independent center reading; ORR, overall response rate; DCR, disease control rate; DoR, duration of response; TTR, time to response.
NCT:04012606

PFS by Investigator per RECIST v1.1

Final PFS analysis data cutoff date: February 28, 2022; median follow-up of 11.8 months



	No. of events/total No. of patients	Median PFS, months (95% CI)	1-Yr PFS rate, % (95% CI)
Toripalimab + chemotherapy	171/223	5.8 (5.6, 6.8)	18.1 (12.9, 24.0)
Placebo + chemotherapy	190/219	5.6 (5.5, 5.7)	4.9 (2.4, 8.8)

Stratified HR for disease progression or death
0.667 (95% CI 0.539, 0.824)
P = 0.0002

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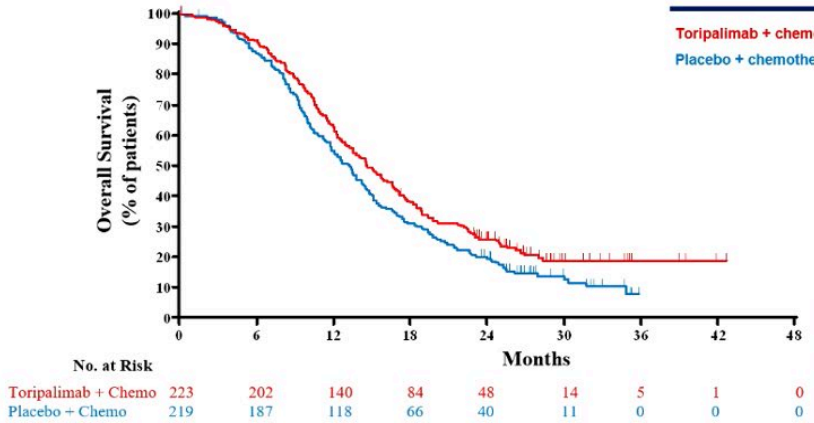
EXTENTORCH: Randomized phase III of toripalimab vs placebo in combination with chemotherapy as 1st line in EE-SCLC

Iniciativa científica de: GECP lung cancer research

Overall Survival

Final OS analysis data cutoff date: April 20, 2023; median follow-up of 13.7 months



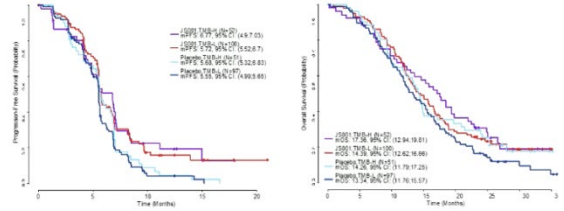
	No. of events/total No. of patients	Median OS, months (95% CI)	1-Yr OS rate, % (95% CI)
Toripalimab + chemotherapy	174/223	14.6 (12.9, 16.6)	63.1 (56.4, 69.0)
Placebo + chemotherapy	187/219	13.3 (11.8, 14.4)	54.9 (48.0, 61.3)

Stratified HR for death
0.798 (95% CI 0.648, 0.982)
P = 0.0327

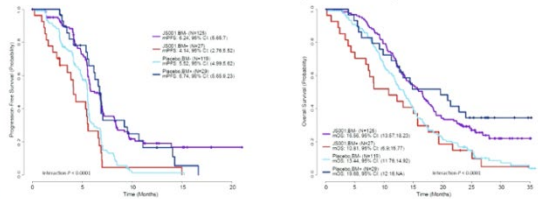
Follow-up antitumor therapy	Toripalimab + chemotherapy N=223, n (%)	Placebo + chemotherapy N=219, n (%)
Any systemic therapy	123 (55.2)	152 (69.4)
PD-(L)1 inhibitor	31 (13.9)	56 (25.6)
TKI*	75 (33.6)	97 (44.3)
Chemotherapy	110 (49.3)	130 (59.4)
≥ Third-line therapy	88 (39.5)	130 (59.4)

Biomarkers Analysis

TMB was Not a Predictive Marker of PFS/OS



Pts with Mutations in Focal Adhesion/Integrin Pathway Benefited Less from ICI



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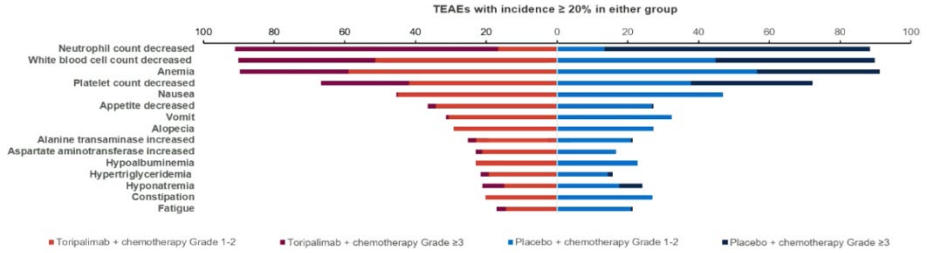
Safety Overview

Patients [a], n (%)	Toripalimab + chemotherapy (N=222)		Placebo + chemotherapy (N=216)	
	Any grade	Grade≥3	Any grade	Grade≥3
Any TEAEs [b,c]	221 (99.5)	199 (89.6)	216 (100)	193 (89.4)
Immune-related AEs [c]	64 (28.8)	22 (9.9)	24 (11.1)	2 (0.9)
leading to discontinuation [d]	7 (3.2)	6 (2.7)	7 (3.2)	6 (2.8)
Infusion reactions	8 (3.6)	0 (0)	1 (0.5)	0 (0)
Fatal AEs	12 (5.4)	12 (5.4)	7 (3.2)	7 (3.2)



[a] Patients received at least 1 dose of the study drug.; [b] TEAE, treatment-emergent adverse event; [c] Based on investigator's assessment. [d] TEAE led to discontinuation of all medications
Data cutoff date: April 20, 2023.

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Estudios fase III de Anti-PD1/PDL1 + Quimioterapia 1ª línea EE-SCLC

Iniciativa científica de: GECP lung cancer research

	Impower 133 Atezolizumab (ant- PD-L1)	CASPIAN Durvalumab (anti-PD-L1)	Capstone-1 Adebrelimab (anti PD-L1)	KN604 Pembrolizumab (anti- PD-1)	ASTRUM-005 Serplulimab (anti-PD-1)	RATIONALE -312 Tislelizumab (anti- PD-1)	EXTENTORCH Toripalimab (anti-PD-1)
N	403	805	462	453	585	457	442
mSG QT-IO/QT-Pcb **HR (95% IC)** **36 meses** **60 meses**	12.3/10.3 m 0.76 (0.60-0.95) 16%/NE 12%/NE	12.9/10.5 m 0.71 M(0.60-0.86) 17.6%/5.8% NE	15.3/12.8 m 0.72 (0.58-0.90) NE NE	10.8/9.7 m 0.76 ,(0.63-0.93) 15.5%/5.9% NE	15.4/10.9 m 0.63 (0.49-0.82) NE NE	15.5/13.5 0.75 (0.61-0.92) NE NE	14.6/13.3 0.798 (0.648-0.982) NE NE
mSLP **HR (95% IC)**	5.2/4.3 m 0.77 (0.62-0.93)	5.1/5.4 0.80 (0.66-0.96)	5.8/5.6 0.67 (0.54-0.83)	4.5/4.3 0.75 (0.61-0.91)	5.7/4.3 0.48 (0.38-0.59)	4.8/4.3 0.63 (0.51-0.78)	5.9/5.6 0.667 (0.539 -0.824)
RG **mDR,**	60.2/64.4% 4.2/3.9 m	68/58% 5.1/5.1 m	70.4/65.9% 5.6/4.6 m	70.6%/61.8% 4.2/3.7 m	80.2%/70.4% 5.6/3.2 m	68.3%/61.7% 4.3/4.7 m	NR NR

mSG: mediana Supervivencia Global, mSLP: mediana supervivencia libre de progresión, RG: Respuestas globales, DR: duración respuestas, NE: no evaluado, NR: no reportado

Lurbidectidine in combination with pembrolizumab in relapsed SCLC. The Phase I/II LUPER Study

Iniciativa científica de: GECP lung cancer research

- The primary objective in the Phase II stage is to assess the efficacy of lurbinectedin with pembrolizumab in terms of ORR, according to RECIST v.1.1, in patients with relapsed SCLC
- Secondary endpoints include investigator-assessed DoR, PFS, OS, and safety per CTCAE 5.0

Key Inclusion Criteria

- ≥18 years old
- Histologically confirmed SCLC
- Progression after 1L platinum-based CT
- No prior exposure to immunotherapy
- ECOG PS of 0-1
- Measurable disease as per RECIST 1.1.
- Brain metastasis allowed if treated and asymptomatic

Phase 1
Dose-ranging
n=13

Starting doses: Lurbinectedin at 2.4 mg/m² IV Q3W + pembrolizumab 200 mg IV Q3W

Interim analysis

Phase 2
Non-randomized expansion
Total n=28

RP2D: Lurbinectedin at 3.2 mg/m² IV Q3W + pembrolizumab 200 mg IV Q3W without prophylactic G-CSF [3]

[1] García-Campelo, R., et al. Clin Transl Oncol (2023) 25(9):2679-2691.
[2] Singh, S., et al. Clin Cancer Res (2021) 27 (9): 2378–2382.
[3] Calles, A., et al. ASCO (2022)

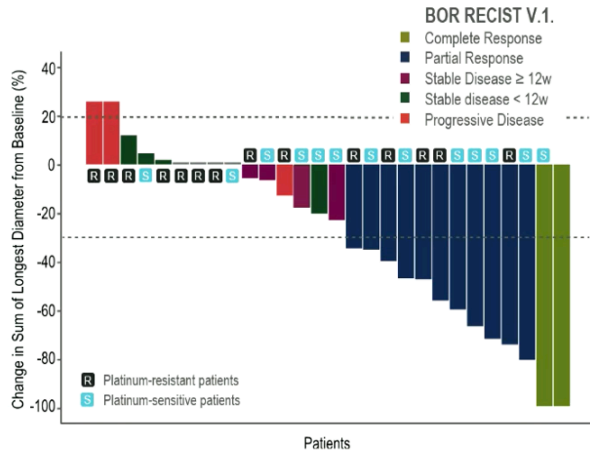
Antonio Calles, et al. ESMO 23

Results

Objective Response Rate (ORR) by RECIST v.1.1

The primary objective has been achieved with 46.4% confirmed response rate assessed by investigator (95% CI: 29.5–64.2; p < 0.001)

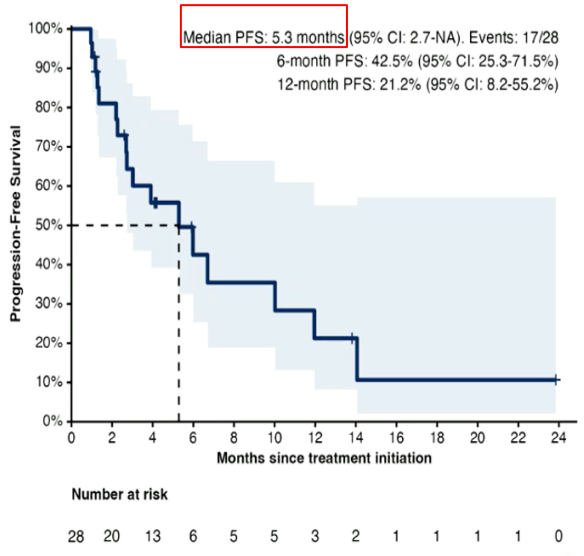
Tumor response, n (%)	Platinum-free interval <90 days (n = 14)	Platinum-free interval ≥90 days (n = 13)	Overall (N = 28)
Best Overall Response			
CR*	0 (0%)	1 (7.7%)	2 (7.1%)
PR	5 (35.7%)	6 (46.2%)	11 (39.3%)
SD ≥ 12w	1 (7.1%)	3 (23.1%)	4 (14.3%)
SD < 12w	2 (14.3%)	2 (15.4%)	4 (14.3%)
PD	3 (21.4%)	0 (0%)	3 (10.7%)
NE	3 (21.4%)	1 (7.7%)	4 (14.3%)
Objective Response Rate			
Yes*	5 (35.7%)	7 (53.9%)	13 (46.4%)
No	9 (64.3%)	6 (46.1%)	15 (53.6%)
Clinical Benefit Rate			
Yes*	6 (42.9%)	10 (76.9%)	17 (60.7%)
No	8 (57.1%)	3 (23.1%)	11 (39.3%)

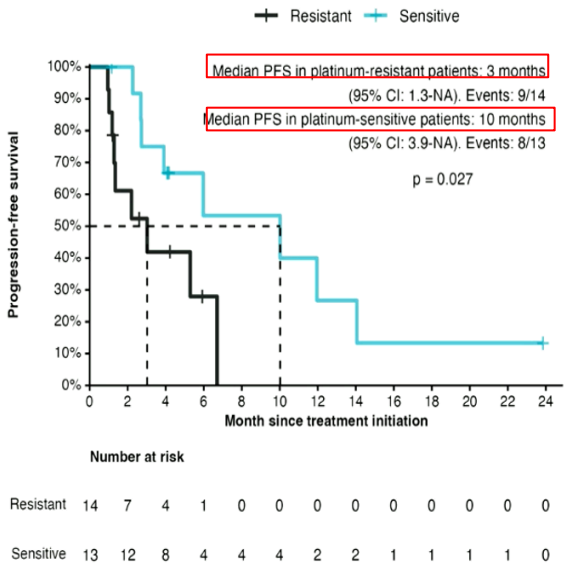


n (%), number of patients (percentage based on N); N, number of patients in the population; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; NE: Not evaluated. *Information on the platinum-free interval of patient 0102-004 is missing. This patient had a BOR = CR.

Results

Progression-Free Survival (PFS)





Lurbidectidine in combination with pembrolizumab in relapsed SCLC. The Phase I/II LUPER Study

Iniciativa científica de: GECP lung cancer

Safety analysis

Results

Safety Analysis of TEAEs Affecting ≥10% of Patients

	TEAE (N = 28)		
Adverse events, n (%)	Any grade	Grade 3	Grade 4
ANY	28 (100%)	21 (75%)	7 (25%)
HEMATOLOGICAL	23 (82.1%)	15 (53.6%)	7 (25%)
Neutropenia	19 (67.9%)	11 (39.3%)	7 (25%)
Anaemia	11 (39.3%)	3 (10.7%)	0 (0%)
Thrombocytopenia	8 (28.6%)	2 (7.1%)	0 (0%)
Lymphopenia	6 (21.4%)	2 (7.1%)	0 (0%)
NON-HEMATOLOGICAL	28 (100%)	12 (42.9%)	0 (0%)
Fatigue	20 (71.4%)	2 (7.1%)	0 (0%)
Nausea	11 (39.3%)	0 (0%)	0 (0%)
Decreased appetite	11 (39.3%)	0 (0%)	0 (0%)
Alanine aminotransferase increased	11 (39.3%)	4 (14.3%)	0 (0%)
Aspartate aminotransferase increased	10 (35.7%)	2 (7.1%)	0 (0%)
Vomiting	8 (28.6%)	0 (0%)	0 (0%)
Pyrexia	7 (25%)	1 (3.6%)	0 (0%)
Constipation	7 (25%)	0 (0%)	0 (0%)

	TEAE (N = 28)		
Adverse events, n (%)	Any grade	Grade 3	Grade 4
ANY	28 (100%)	21 (75%)	7 (25%)
NON-HEMATOLOGICAL	28 (100%)	12 (42.9%)	0 (0%)
Dyspnoea	7 (25%)	0 (0%)	0 (0%)
Cough	6 (21.4%)	0 (0%)	0 (0%)
Diarrhoea	5 (17.9%)	0 (0%)	0 (0%)
Arthralgia	5 (17.9%)	0 (0%)	0 (0%)
Pneumonia	4 (14.3%)	3 (10.7%)	0 (0%)
Myalgia	4 (14.3%)	0 (0%)	0 (0%)
Dysgeusia	4 (14.3%)	0 (0%)	0 (0%)
Hyperglycaemia	3 (10.7%)	0 (0%)	0 (0%)
Weight decreased	3 (10.7%)	0 (0%)	0 (0%)
Blood triglycerides increased	3 (10.7%)	0 (0%)	0 (0%)
Pain in extremity	3 (10.7%)	0 (0%)	0 (0%)
Chest pain	3 (10.7%)	0 (0%)	0 (0%)
Abdominal pain	3 (10.7%)	0 (0%)	0 (0%)

n (%), number of patients (percentage based on *N*), *N*, number of patients in the population; TEAE: Treatment emergent adverse events

Results

Safety Analysis of Immune-Related TEAEs

	TEAE		
Adverse events, n (%)	Any grade	Grade 3	Grade 4
ANY	15 (53.6%)	5 (17.9%)	0 (0%)
NON-HEMATOLOGICAL	15 (53.6%)	5 (17.9%)	0 (0%)
Pneumonitis	1 (3.6%)	0 (0%)	0 (0%)
Diarrhoea	5 (17.9%)	0 (0%)	0 (0%)
Aspartate aminotransferase increased	11 (39.3%)	4 (14.3%)	0 (0%)
Alanine aminotransferase increased	10 (35.7)%	2 (7.1%)	0 (0%)
Blood bilirubin increased	3 (10.7%)	0 (0%)	0 (0%)
Hyperthyroidism	1 (3.6%)	0 (0%)	0 (0%)
Hypothyroidism	2 (7.1%)	0 (0%)	0 (0%)
Blood creatinine increased	1 (3.6%)	0 (0%)	0 (0%)
Renal failure	1 (3.6%)	1 (3.6%)	0 (0%)
Neuropathy peripheral	1 (3.6%)	0 (0%)	0 (0%)

n (%), number of patients (percentage based on *N*), *N*, number of patients in the population; TEAE: Treatment emergent adverse events

Lurbidectidine in combination with pembrolizumab in relapsed SCLC. The Phase I/II LUPER Study

Iniciativa científica de: GECP lung cancer research

- The combination lurbinectedine + pembrolizumab (46,4% RR) is an effective second line for SCLC patients who did not receive inmmunotherapy

- mPFS was significantly longer for sensitive vs resistant patients (10 vs 3 months)

LUPER in the contest of relapsed SCLC treatment

Indirect comparison with other second-line options

Study	Ref	#Pts	RR%	PFS (mo)	RR% Ref	PFS Ref (mo)	RR% Sen	PFS Sen (mo)
Lurbi+Pembro (Ph 1-2)	Calles (ESMO'23)	28	46.4	5.3	35.7	3.0	53.9	10.0
Lurbi single agent (Ph 2)	Trigo (LO'20)	105	35.2	3.5	22.0	2.6	45.0	4.6
Pembro single agent (Ph 2)	Chung (ASCO'18)	107	18.7	2.0	-	-	-	-
Lurbi + Doxo (Ph 3)	Aix (Lancet RM'23)	307	32.0	4.0	-	-	-	-
Platinum + etoposide (Ph 3)	Baize (LO'20)	81	-	-	-	-	49%	4.7

Tarlatamab in pretreated SCLC. Primary results of the phase II trial DeLLphi-301 study

Iniciativa científica de: GECP lung cancer research

33% ≧ 3 lines
Previous IO 73%

Luis Paz Ares et, al. ESM023

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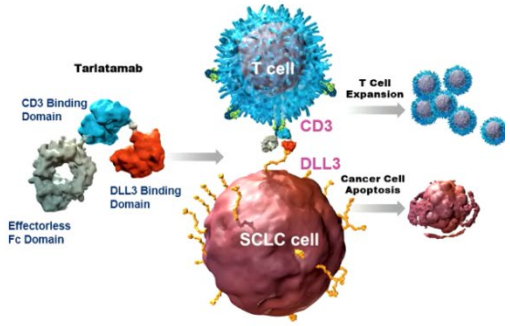
Iniciativa científica de: GECP lung cancer research

Background

- Small cell lung cancer (SCLC) is an aggressive disease with poor survival outcomes and no approved therapies in the third-line and beyond[1–3]
- Tarlatamab is a BiTE® (bispecific T-cell engager) immunotherapy that binds to both delta-like ligand 3 (DLL3) on SCLC cells and CD3 on T cells, leading to T cell-mediated cancer cell lysis[4]
- Tarlatamab showed manageable safety and promising antitumor activity in a phase 1 study in previously treated SCLC[5]



Tarlatamab activates T cells without relying on MHC-I

Here, we present the phase 2 DeLLphi-301 study of tarlatamab in patients with advanced SCLC previously treated with 2 or more lines of therapy

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CD3, cluster of differentiation 3; Fc, fragment crystallizable; MHC-I, major histocompatibility complex-I.

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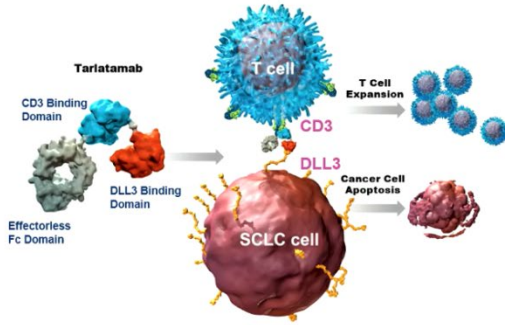

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DeLLphi-301 Study Design

Phase 2, open-label study (NCT05060016)

Key Inclusion Criteria

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

R 1:1

Part 1: Dose Evaluation

- Tarlatamab 10 mg (n = 88): 1 mg on Day 1, followed by 10 mg on Days 8, 15, and Q2W thereafter
- Tarlatamab 100 mg (n = 88): 1 mg on Day 1, followed by 100 mg on Days 8, 15, and Q2W thereafter

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

33% ≧ 3 lines
Previous IO 73%

Primary Endpoint: ORR per RECIST v1.1 by BICR, TEAEs, tarlatamab serum concentrations
Secondary Endpoints Included: DOR, DCR, PFS per RECIST v1.1 by BICR, OS

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*Once 30 patients per dose level had the opportunity to confirm an objective response after the first post-treatment scan or ≥ 13 weeks of follow-up, whichever occurred first.
BICR, blinded independent central review; **DCR**, disease control rate; **DOR**, duration of response; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **ES-SCLC**, extensive stage-small cell lung cancer; **ITT**, intention-to-treat; **ORR**, objective response rate; **OS**, overall survival; **PFS**, progression-free survival; **Q2W**, every 2 weeks; **R**, randomization; **RECIST**, Response Evaluation Criteria in Solid Tumors; **TEAE**, treatment-emergent adverse event.

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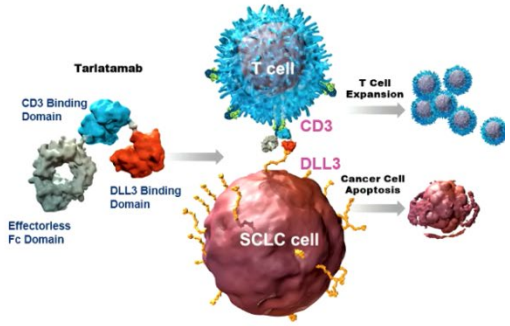

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DeLLphi-301 Study Design

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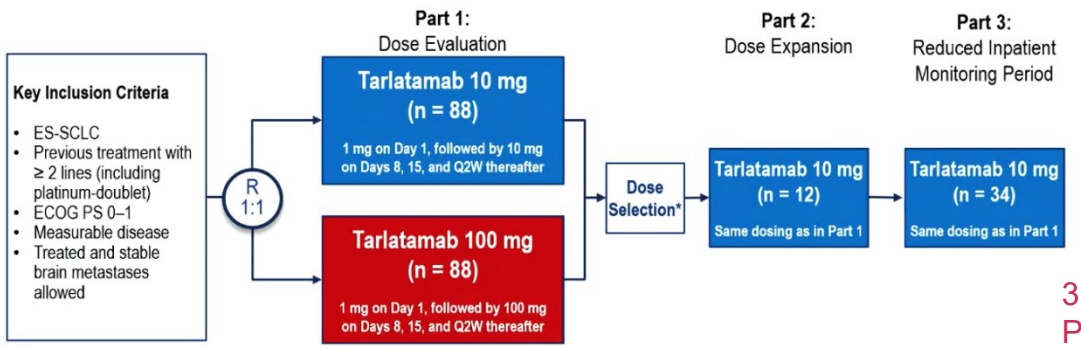

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BICR, blinded independent central review; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ES-SCLC, extensive stage-small cell lung cancer; ITT, intention-to-treat; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q2W, every 2 weeks; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; TEAE, treatment-emergent adverse event.

4

Tarlatamab Anti-Tumor Activity

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	1 (1)	7 (8)
Partial response	39 (39)	21 (24)
Stable disease	30 (30)	27 (31)
Progressive disease	20 (20)	13 (15)
Not evaluable / no post-baseline scan*	10 (10)	20 (23)
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)

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

Luis Paz Ares et, al. ESM023

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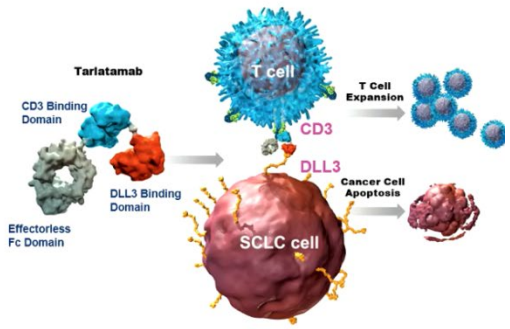
- Tarlatamab is a BiTE® (bispecific T-cell engager) immunotherapy that binds to both delta-like ligand 3 (DLL3) on SCLC cells and CD3 on T cells, leading to T cell-mediated cancer cell lysis[4]
- Tarlatamab showed manageable safety and promising antitumor activity in a phase 1 study in previously treated SCLC[5]

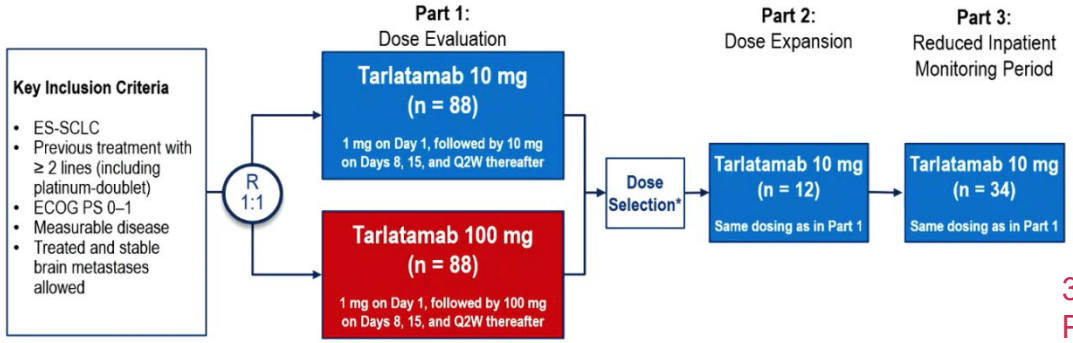


Tarlatamab activates T cells without relying on MHC-I

Here, we present the phase 2 DeLLphi-301 study of tarlatamab in patients with advanced SCLC previously treated with 2 or more lines of therapy

DeLLphi-301 Study Design

Phase 2, open-label study (NCT05060016)



33% ≧ 3 lines
Previous IO 73%

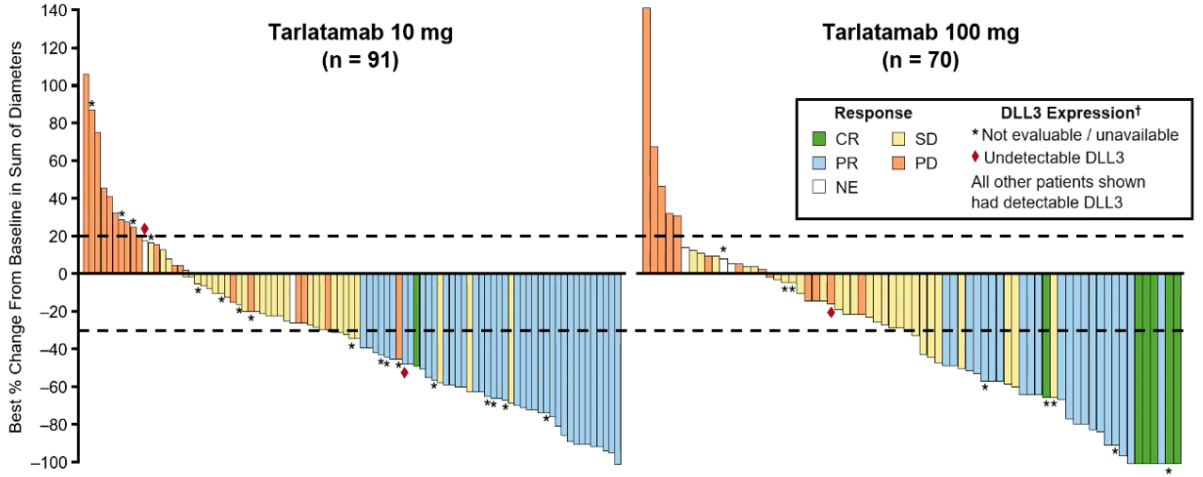
Primary Endpoint: ORR per RECIST v1.1 by BICR, TEAEs, tarlatamab serum concentrations
Secondary Endpoints Included: DOR, DCR, PFS per RECIST v1.1 by BICR, OS

Tarlatamab Anti-Tumor Activity

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	1 (1)	7 (8)
Partial response	39 (39)	21 (24)
Stable disease	30 (30)	27 (31)
Progressive disease	20 (20)	13 (15)
Not evaluable / no post-baseline scan*	10 (10)	20 (23)
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)

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

Anti-tumor Activity



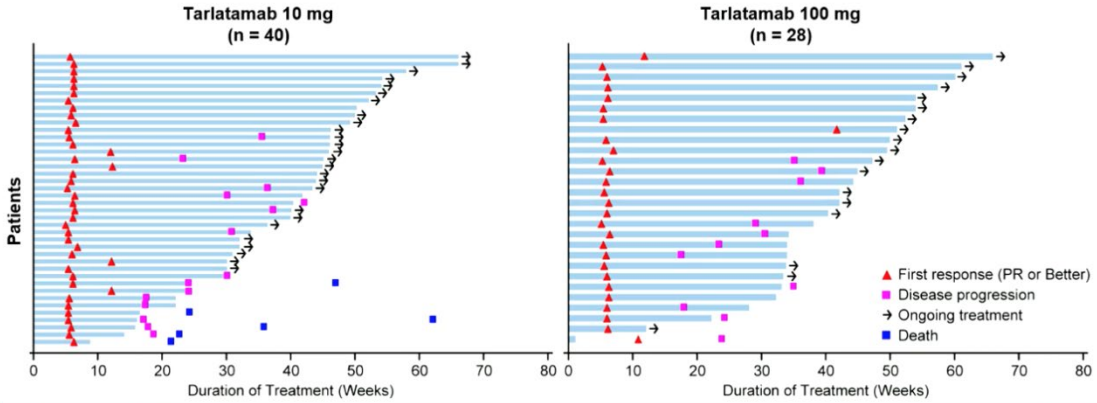
Responses were observed regardless of DLL3 expression, as well as in patients without evaluable tumor tissue

Luis Paz Ares et, al. ESM023

Tarlatamab in pretreated SCLC. Primary results of the phase II trial DeLLphi-301 study

Iniciativa científica de:

Duration of Response and Treatment



- Median TTR was 1.4 months (range, 1.1–9.6 months), and median DOR was not reached
- Of the 68 responders, the DOR was ≥ 6 months in 40 patients (59%)
- 56% of the responses were ongoing at data cutoff

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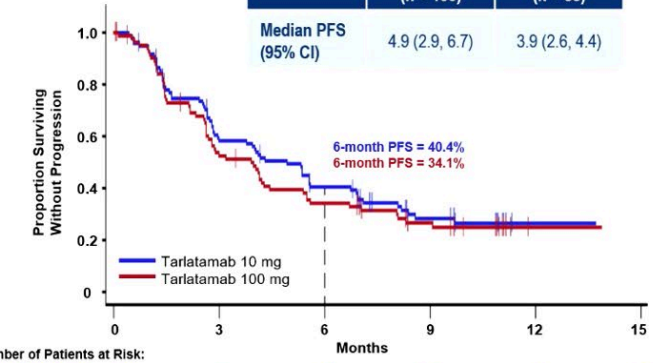
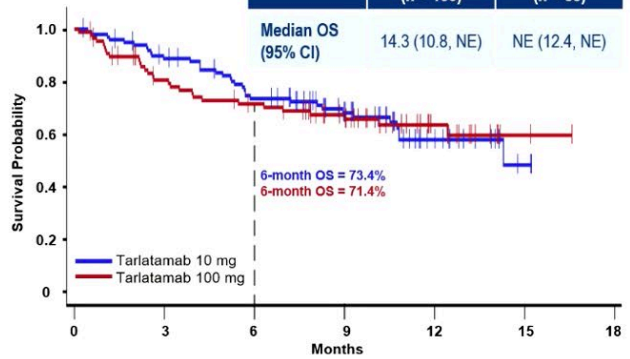
Median follow-up time for DOR, 9.5 months (95% CI; 8.3, 9.7 months).
DOR, duration of response; PR, partial response; TTR, time to objective response.

PFS and OS

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



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



Number of Patients at Risk:

Tarlatamab 10 mg	100	53	35	18	2	0	100	84	67	44	17	3	0
Tarlatamab 100 mg	88	41	26	15	3	0	88	62	53	39	16	2	0

- 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

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

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Summary of Adverse Events*

TEAEs, n (%)	Part 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, n (%)	Part 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)
Grade 1–2	49 (49)	48 (55)	18 (53)
≥ Grade 3	0	5 (6)	1 (3)
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 favorable safety profile, with a low rate of discontinuations due to treatment-related adverse events (TRAEs)
- Shorter inpatient monitoring (Part 3) did not alter the safety profile

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*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). †Fatal TRAE was respiratory failure.
CRS, cytokine release syndrome; TEAE, treatment-emergent adverse event.

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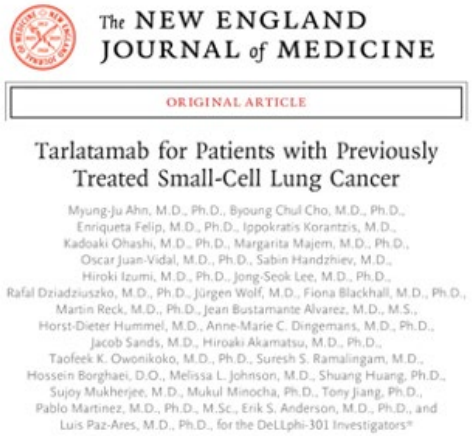
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tarlatamab for Patients with Previously Treated Small-Cell Lung Cancer

Myung-Ju Ahn, M.D., Ph.D., Byoung Chul Cho, M.D., Ph.D., Enriqueta Felip, M.D., Ph.D., Ippokratis Korantzis, M.D., Kadoaki Ohashi, M.D., Ph.D., Margarita Majem, M.D., Ph.D., Oscar Juan-Vidal, M.D., Ph.D., Sabin Handzhiev, M.D., Hiroki Izumi, M.D., Ph.D., Jong-Seok Lee, M.D., Ph.D., Rafal Dziadziuszko, M.D., Ph.D., Jürgen Wolf, M.D., Fiona Blackhall, M.D., Ph.D., Martin Reck, M.D., Ph.D., Jean Bustamante Alvarez, M.D., M.S., Horst-Dieter Hummel, M.D., Anne-Marie C. Dingemans, M.D., Ph.D., Jacob Sands, M.D., Hiroaki Akamatsu, M.D., Ph.D., Taofeek K. Owonikoko, M.D., Ph.D., Suresh S. Ramalingam, M.D., Hossein Borghaei, D.O., Melissa L. Johnson, M.D., Shuang Huang, Ph.D., Sujoy Mukherjee, M.D., Mukul Minocha, Ph.D., Tony Jiang, Ph.D., Pablo Martinez, M.D., Ph.D., M.Sc., Erik S. Anderson, M.D., Ph.D., and Luis Paz-Ares, M.D., Ph.D., for the DeLLphi-301 Investigators*

CRS was largely confined to 1st & 2 course and primarily Grade 1 & 2
ICANS: Inmmune-efector cell associated neurotoxicity síndrome 7% (10mg) 28% (100 mg)

Luis Paz Ares et, al. ESM023

Tarlatamab in pretreated SCLC. Primary results of the phase II trial DeLLphi-301 study

iniciativa científica de: GECP lung cancer research

Encouraging and duration of responses.Results support the use of tarlatamab in previously treated SCLC.

Ongoing Ph III trial DeLLphi-304 comparing tarlatamab vs standard treatment

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Outcomes comparison in pretreated SCLC

Drug	Dose	Line	Study	N	ORR (%)	DoR months	mPFS months	mOS months
Tarlatamab DeLLPhi-301 *Paz Ares L, ESMO 2023*	10 100	33% ≥ 3L 43% ≥ 3L	II	100 88	40 32	58% ≥ 6 mo 61% ≥ 6 mo	4.9 3.9	14.3 NE (12.4, NE)
Tarlatamab DeLLphi-300 *Paz Ares L, JCO 2023*	several	30% ≥ 3 L	FIH	107	23	12.3	3.7	13.2
BI764532 (DLL3+) *Wermke M. WCLC 2023*	≥ 90µg/kg	31% ≥ 3 L	I	39 SCLC	26	Too early	NA	NA
HPN328 *Johnson M, ASCO 2022*	≥ 1215mg	Median 3L	I/IIa	10 SCLC	40 (2/4 pat)	Too early	NA	NA
I-Dxd; DS-7300 *Johnson M, WCLC 2023*	≥6.4mg/kg	Median 2 L	I/II	22 SCLC	52.4	5.9	5.6	12.2
Rova-T Tahoe (DLL3 > 75% expression) *Blackhall F, JTO 2021*		2 line	III	287 RovaT 119 Topo	15 21	3.5 4.9	3 4.3	6.3 8.6
Lurbinectidin *Trigo JM, Lancet Oncology 2020*	3.2 mg/m^2	7% 2 prior L	II	105	35	5.3	3.5	9.3
Lurbinectidin + Doxo Vs control arm (Atlantis) *Ponce S, Lancet Respir Med 2023*	2 + 40 mg/m^2	2 line	III	307 306	32 30	5.7 3.8	4.2 4.1	9 7.7

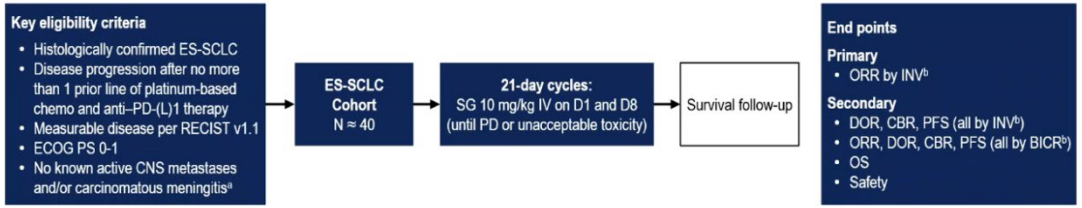
I-Dxd DS-7300 Ifinatamab- deuxtecan: ADC contra B7-H3

Sacizutumab-govitecan as second-line treatment in ES-SCLC

Iniciativa científica de: GECP lung cancer research

Background and study design

- Treatment options for patients with relapsed SCLC are limited[1]
- Sacituzumab govitecan is a Trop-2–directed ADC approved globally for the treatment of 2L+ mTNBC and pretreated HR+/HER2– mBC[2,3] and received accelerated approval in the United States for 2L mUC[3]
- The ongoing, open-label, multicohort, phase 2 TROPiCS-03 study (NCT03964727) is evaluating SG in patients with metastatic or locally advanced solid tumors



- At data cutoff (27 July 2023), median follow-up was 5.1 months (range, 1.9-12.2)

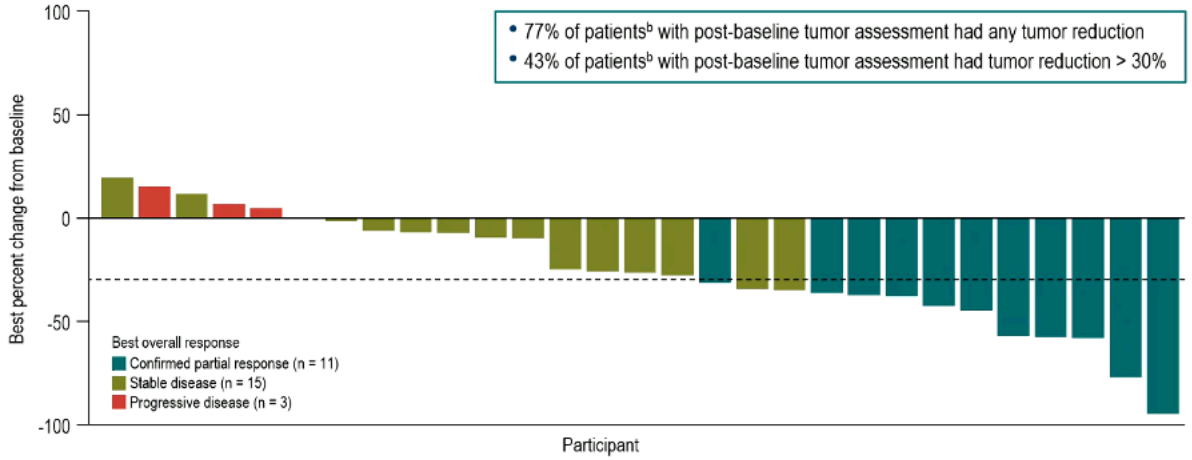
2L, second-line; ADC, antibody-drug conjugate; BICR, blinded independent central review; CBR, clinical benefit rate; CNS, central nervous system; D, day; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ES-SCLC, extensive stage small cell lung cancer; HER2–, human epidermal growth factor receptor 2-negative; HR+, hormonal receptor-positive; INV, investigator; IV, intravenous; mBC, metastatic breast cancer; mTNBC, metastatic triple-negative breast cancer; mUC, metastatic urothelial cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-(L)1, programmed death (ligand) 1; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SCLC, small cell lung cancer; SG, sacituzumab govitecan; Trop-2, trophoblast cell surface antigen 2. [a]Patients with stable CNS disease for at least 4 weeks prior to the first study dose and all neurologic symptoms returned to baseline may be included in the study. All patients with carcinomatous meningitis are excluded from the study regardless of clinical stability. [b]Per RECIST v1.1. **1.** Dingemans AC, et al. *Ann Oncol*. 2021;32(7):839-853. **2.** TRODELVY® (sacituzumab govitecan-hziy) [summary of product characteristics]. Gilead Sciences Ireland UC, Carrigtohill, Ireland; July 2023. **3.** TRODELVY® (sacituzumab govitecan-hziy) [prescribing information]. Foster City, CA: Gilead Sciences, Inc.; June 2023

Efficacy by investigator assessment

Efficacy by INV[a]	ES-SCLC N = 30[b]
ORR [Confirmed CR + PR] **(95% CI), %**	37 (20-56)
BOR, n (%)	
Confirmed PR	11 (37)
SD	15 (50)
PD	3 (10)
DCR [Confirmed CR + PR + SD] **(95% CI), %**	87 (69-96)
CBR [Confirmed CR + PR + SD ≥ 6 months] **(95% CI), %**	40 (23-59)
Median DOR (95% CI),[c,d] months	6.3 (2.7-NR)
DOR rate at 6 months (95% CI),[c,d] %	63 (14-89)

Patients without post-baseline response assessments were counted as not assessed (n = 1). BOR, best overall response; CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DOR, duration of response; ES-SCLC, extensive-stage small cell lung cancer; INV, investigator assessment; NR, not reached; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease. [a]Per RECIST v1.1. [b]Includes patients enrolled on or before 27 April 2023. [c]Evaluated in patients with a confirmed CR or PR. [d]Based on Kaplan-Meier estimates.

Best percent change from baseline in target lesions[a]

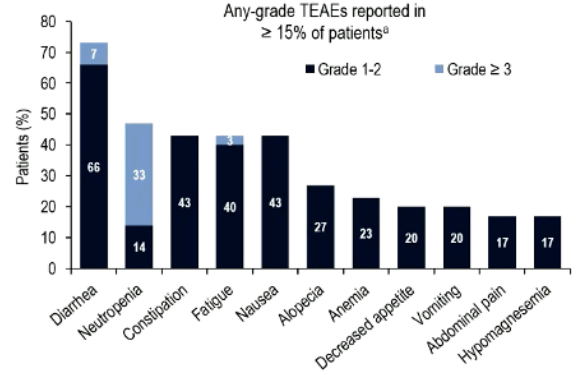


Includes patients enrolled on or before 27 April 2023. RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1. [a]By investigator assessment per RECIST v1.1. [b]Percentages were calculated using the total number of patients (N = 30).

Safety summary

The adverse event profile observed in this trial was consistent with the observed safety of SG in other tumor types

Safety-evaluable patients, n (%)	ES-SCLC N = 30[a]
Any-grade TEAEs	30 (100)
Related to study treatment	28 (93)
Grade ≥ 3 TEAEs	18 (60)
Related to study treatment	15 (50)
Serious TEAEs	9 (30)
Related to study treatment	4 (13)
TEAEs leading to dose reduction	8 (27)
TEAEs leading to discontinuation	0
Related to study treatment	0
TEAEs leading to death	0
Related to study treatment	0



TEAE is defined as any adverse event with an onset date on or after the study treatment start date and no later than 30 days after the last dose of study treatment. ES-SCLC, extensive-stage squamous cell lung cancer; SG, sacituzumab govitecan; TEAE, treatment-emergent adverse event. [a]Includes patients enrolled on or before 27 April 2023.

Sacizutumab-govitecan as second-line treatment in ES-SCLC

Iniciativa científica de: GECP lung cancer research

- SG demonstrated promising efficacy as second-line treatment for patients with ES-SCLC
  - Confirmed ORR was 37%; DOR rate at 6 months was 63%
  - DCR (Confirmed CR + PR + SD) was 87%

TROPIC in the contest of relapsed SCLC treatment

Indirect comparison with other second/further-line options

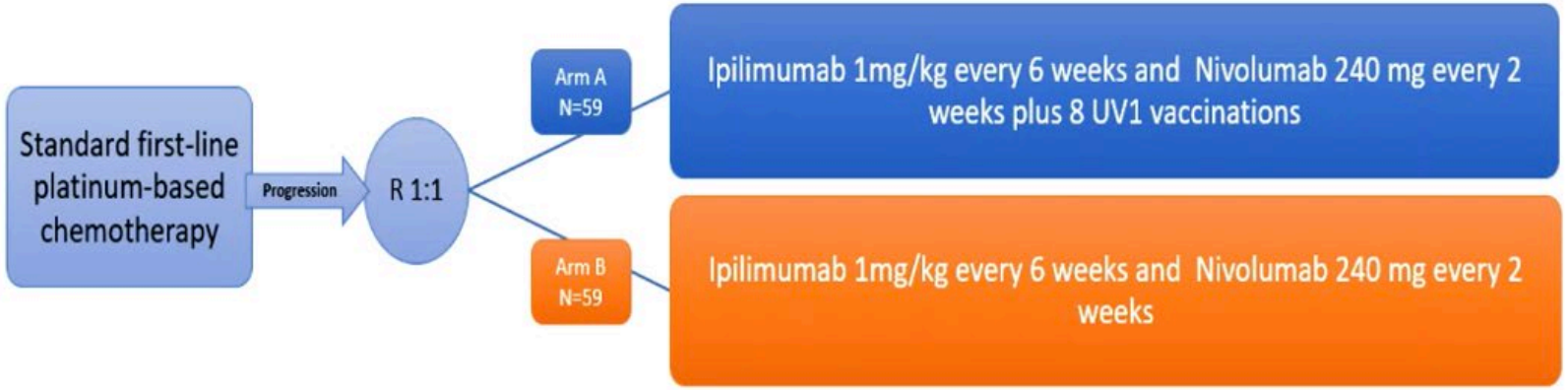
Study	Ref	Drug	Line	# Pts	% RR	mDOR (months)
TROPIC Ph2	Dowlati (ESMO'23)	SG	2nd	30	37	6.3
EORTC Ph2	Ardizzoni (JCO'97)	Topotecan	2nd	92	21.7	7.6
Ph2	Trigo (LO'20)	Lurbinectedin	2nd	105	35.2	5.3
DeLLphi Ph1	Paz Ares (JCO'23)	Tarlatamab	≥2nd	107	23.4	12.3
Ph1	Wermke (WCLC'23)	BI 764532	≥2nd	39	26	NR

First Survival data from the NIPU: randomized phase II trial evaluating Nivo-Ipi with UVI (telomerase vaccination) as second line in malignant mesothelioma

Iniciativa científica de: GECP lung cancer research

Study Design – The NIPU trial, a phase II study

NIPU



*Treatment beyond progression permitted when evidence of clinical benef

Participating sites: Oslo University Hospital (sponsor), Oslo, Norway; Karolinska University Hospital, Stockholm, Sweden; Rigshospitalet, Copenhagen, Denmark; Aalborg University Hospital, Aalborg, Denmark; Vall d'Hebron University Hospital, Barcelona, Spain; Sir Charles Gairdner Hospital, Perth, Aust

Primary endpoint

- PFS by mRECIST, BICR

Secondary endpoints

- OS, ORR, DCR
- QoL
- Toxicity

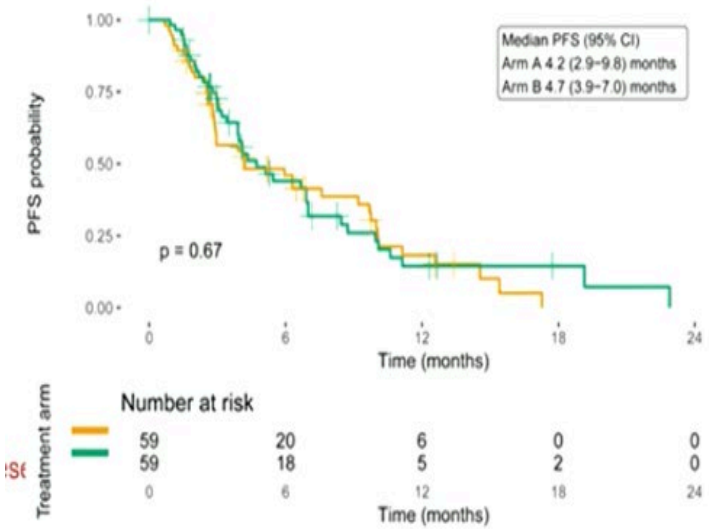
Exploratory endpoints

- Biomarker analyses

Statistics: Sample size estimation based on power 80%, one-sided alpha 0.1, to detect HR 0.6

First Survival data from the NIPU: randomized phase II trial evaluating Nivo-Ipi with UVI (telomerase vaccination) as second line in malignant mesothelioma

Iniciativa científica de: GECP lung cancer research

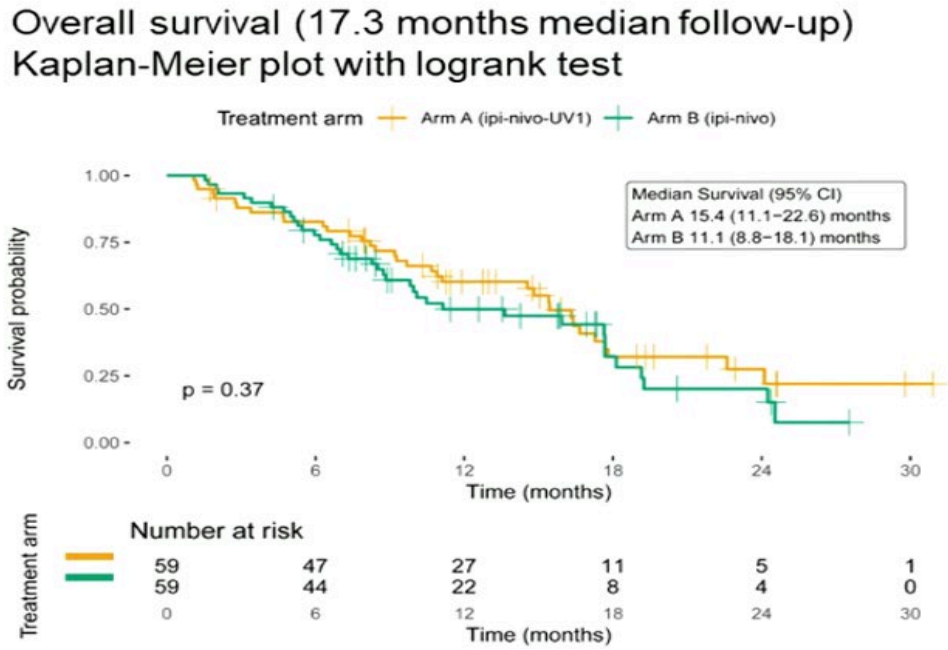


Objective response rate (BICR)

Arm A (ipi-nivo-UV1): 31%

Arm B (ipi-nivo): 16%

Odds Ratio 2.4 (95% CI 1.0-6.3)



How do the data compare to other studies

Ipi/nivo in second line

Study	Setting	n	Histology Epi vs non Epi	Median PFS (95% CI range) months	Median OS	DCR at 12 weeks (95% CI range)
MAPS	Ipi/nivo Non comparative	62	85/15	5,6 (3.1-8.3)	15,9 (10.7-NR)	27 (37-63)
Initiate	Ipi/nivo Single arm	38	86/14	6,2 (4.1, NR)	NR	68 (50-83)
NIPU	Ipi/nivo+UV1	59	75/25	4,2 (2.9-9.8)	15,4 (11.1-22.6)	
	Ipi/nivo	59	80/20	4,7 (3.9-7.0)	11,1 (8.8-18.1)	

#LBA98 Efficacy and safety of ramucirumab plus carboplatin and paclitaxel in untreated metastatic thymic carcinoma: RELEVENT PHASE II Trial

Iniciativa científica de: GECP lung cancer research

- Carboplatin-paclitaxel is the firt-line standard treatmet in TC (RR 36% & mPFS 7.5 m

RELEVENT Study design

Multicentre, IIT, open-label, single arm, phase II study

Key elegibility criteria
- Treatment-naïve advanced or metastatic thymic carcinoma or B3 thymoma with carcinoma areas
- Mesurable disease per RECIST v1.1
- ECOG PS 0-1
- No major standard controindications to antiangiogenics

→

Combination treatment
Ramucirumab 10 mg/kg iv
+ Paclitaxel 200 mg/mq iv
+ Carboplatin AUC5 iv

21-day 6 cycles

→

Mainteance phase
Ramucirumab 10 mg/kg iv

21-day cycles

EOT
Until disease progression, death or unaccettable toxicity

Endpoints
Primary
ORR per RECIST v 1.1

Secondary
DOR per RECIST v1.1
PFS per RECIST v1.1
OS
Safety

At data cut-off (05 October 2023) median follow-up 31.6 months

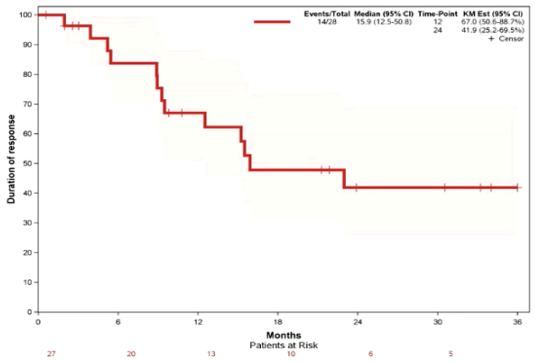
Two-stage Green-Dahlberg statistical plan: The null hypothesis that the true objective response rate (ORR) is 20% (Lemma et al., 2011) had to be tested against a one-sided alternative. In the first stage, 30 patients had to be accrued. If there were 4 or fewer responses in these 30 patients, the study had to be stopped. Otherwise, 25 additional patients had to be accrued for a total of 55. The null hypothesis was rejected if 18 or more responses were observed in 55 patients.
At interim analysis more than the required 18 responses were reported, therefore the accrual was stopped after the enrollment of 35 of the preplanned 55 patients

Efficacy by Investigator Assessment

Response evaluated by Investigator	ITT population N=35
ORR - n (%) [95% CI]	28 (80.0) [63.1 - 91.6]
CR	0 (0.0)
PR	28 (80.0)
SD	7 (20.0)
PD	0 (0.0)
DCR - n (%) [95% CI]	35 (100.0) [90.0 – 100.0]

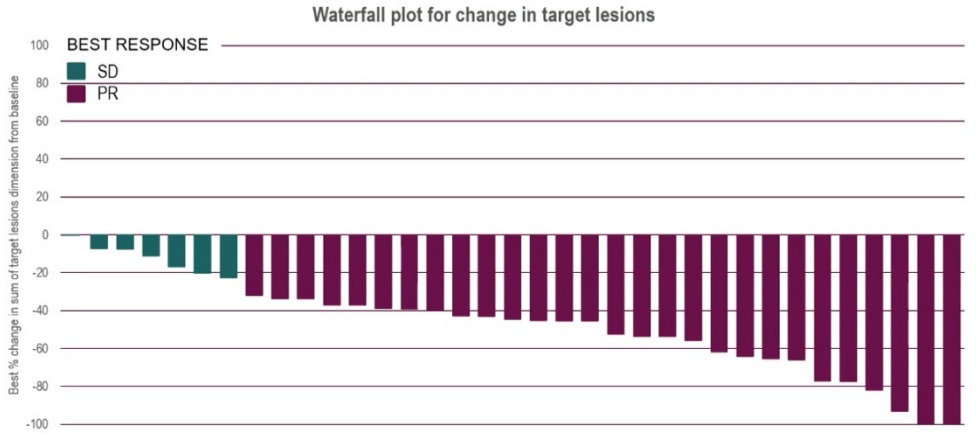
Legend: N: number of subjects. CR: complete response. PR: partial response. SD: stable disease. PD: progressive disease. ORR: objective response rate; DCR: disease control rate;
(*) Patients who did not receive at least one radiological evaluation after study entry

Duration of response (N=28)



Median duration of response:
15.9 [95% CI: 12.5-50.8] months

Depth of response by Investigator Assessment



Claudia Proto, et al. ESMO23

#LBA98 Efficacy and safety of ramucirumab plus carboplatin and paclitaxel in untreated metastatic thymic carcinoma: RELEVENT PHASE II Trial

Iniciativa científica de: GECP

Safety summary

Safety evaluable patients, N (%)	Safety population N=35
Any-grade drug related TEAEs	32 (91.4)
Related to Ramucirumab	25 (71.4)
Grade ≥3 TEAEs	17 (48.6)
Related to Ramucirumab	9 (25.7)
Serious TEAEs	8 (22.8)
Related to Ramucirumab	4 (11.4)
TEAEs leading to treatment discontinuation	8 (22.9)
TEAEs leading to treatment discontinuation of CT	6 (17.1)
TEAEs leading to treatment discontinuation of ramucirumab	7 (20.0)
TEAEs leading to Ramucirumab dose reductions	4 (11.4)
TEAEs leading death	0 (0.0)
Related to study treatment	0 (0.0)

Legend: N: number of subjects. TEAEs: treatment emergent adverse events

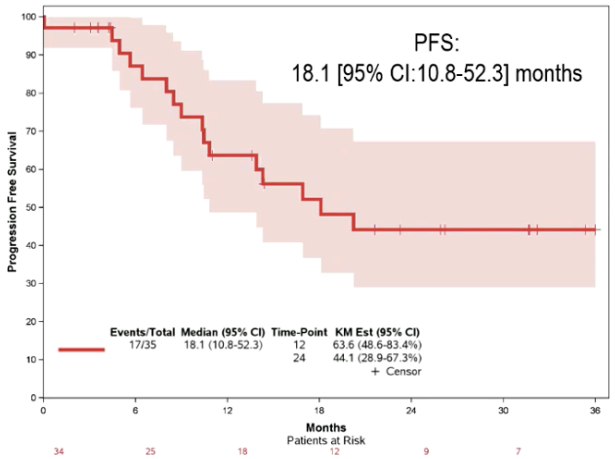
SAE	Grade	Ramucirumab relationship	Outcome
Pulmonary embolism	G4	Yes	Resolved
Arterial haemorrhage	G3	Yes	Resolved
Acute myocardial infarction	G3	Yes	Resolved with sequelae
Acute myocardial infarction	G3	Yes	Resolved

Legend: SAE: serious adverse event; NDR: not drug related

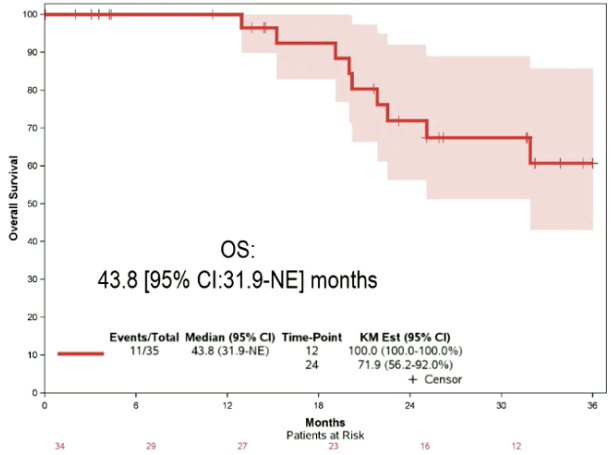
Among the remaining 4 Serious TEAEs, 3 were NDR, 1 was only CT related
All the Serious TEAEs resolved

Efficacy outcomes by Investigator Assessment

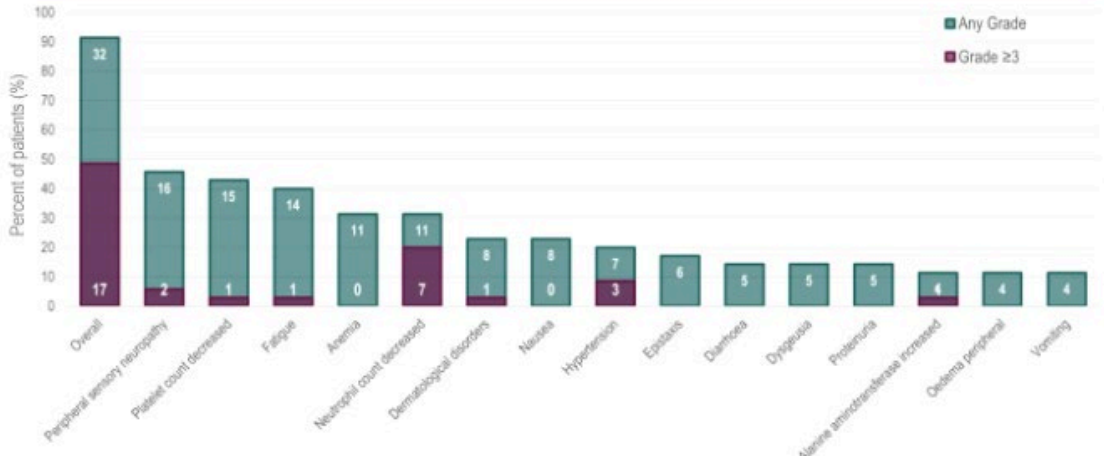
Progression-free Survival (N=35)



Overall Survival (N=35)



TEAES in ≥10% of patients



Conclusions

- ✓Ramucirumab in combination with carboplatin and paclitaxel demonstrates encouraging activity in subjects with untreated TC
  - ORR 80% (95% CI 63.1-91.6) and DCR 100% (95% CI 90-100)
  - Median PFS 18.1 (95% CI 10.8 – 52.3) months and median OS 43.8 (31.9-NE) months
- ✓The combination toxicity profile is manageable and consistent with the known safety of each agent
- ✓Despite this is a non-randomized trial, to our knowledge, the addition of ramucirumab to carboplatin and paclitaxel shows the best activity results in this setting
- ✓ A SWOG phase II trial is investigating carboplatin and paclitaxel with or without ramucirumab as first line treatment in advanced TC

The addition of Ramucirumab to carboplatin and paclitaxel represents a valid first line treatment in advanced TC

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Carboplatin/Paclitaxel first line regimens in thymic carcinoma

	Design	N	ORR %	mPFS mo.	mOS mo.
Paclitaxel/Carboplatin Leman G *J Clin Oncol 2011*	Phase II	23	22	5	20
Paclitaxel/Carboplatin Petat A *Eur J Cancer 2022*	RHYTHM Retrospective	62	53	8	33
Paclitaxel/Carboplatin Ko R *The Oncologist 2018*	NEJ023 Retrospective	70	38	9	28
Paclitaxel/Carboplatin **+ Ramucirumab** *Proto C* *ESMO 2023*	Phase II	**35**	**80**	**18**	**43.8**

RESUMEN

- Toripalimab (anti-PD1) + platino etoposido aumenta significativamente la SG, resultados algo inferiores a estudios previos con AntiPD1/PD-L1 . Son necesarios más estudios me too?. El único estudio que parece mejorar resultados es el estudio con Benmeistobart (anti-PD-1) + PE+ anlotinib, llegando a una mSG de 19.32 meses, necesita validación en paises Occidentales
- En segunda línea la combinación lurbidectedina + pembrolizumab ha mostrado unas RG excelentes: 46,4%, en enfermedad sensible 56.4%
- El anticuerpo bi-específico contra DLL3- CD3 como el tarlatamab produce unas respuestas del 40%, mPFS 4.9%, mOS 14.4 m

- Los anticuerpos conjugados anti- TROP2 y anti B7- H3 muestran resultados muy prometedores con perfil de toxicidad tolerable

- Las vacunas contra el receptor de telomerasas combinado con Nivo-ipi en 2ª línea de mesotelioma no ha cumplido su objetivo primario de SLP

- La combinación carboplatino-taxol- ramucirumab ha obtenido unas RG excelentes del 80%, mSLP DE 18.1 meses y una mSG de 43.8