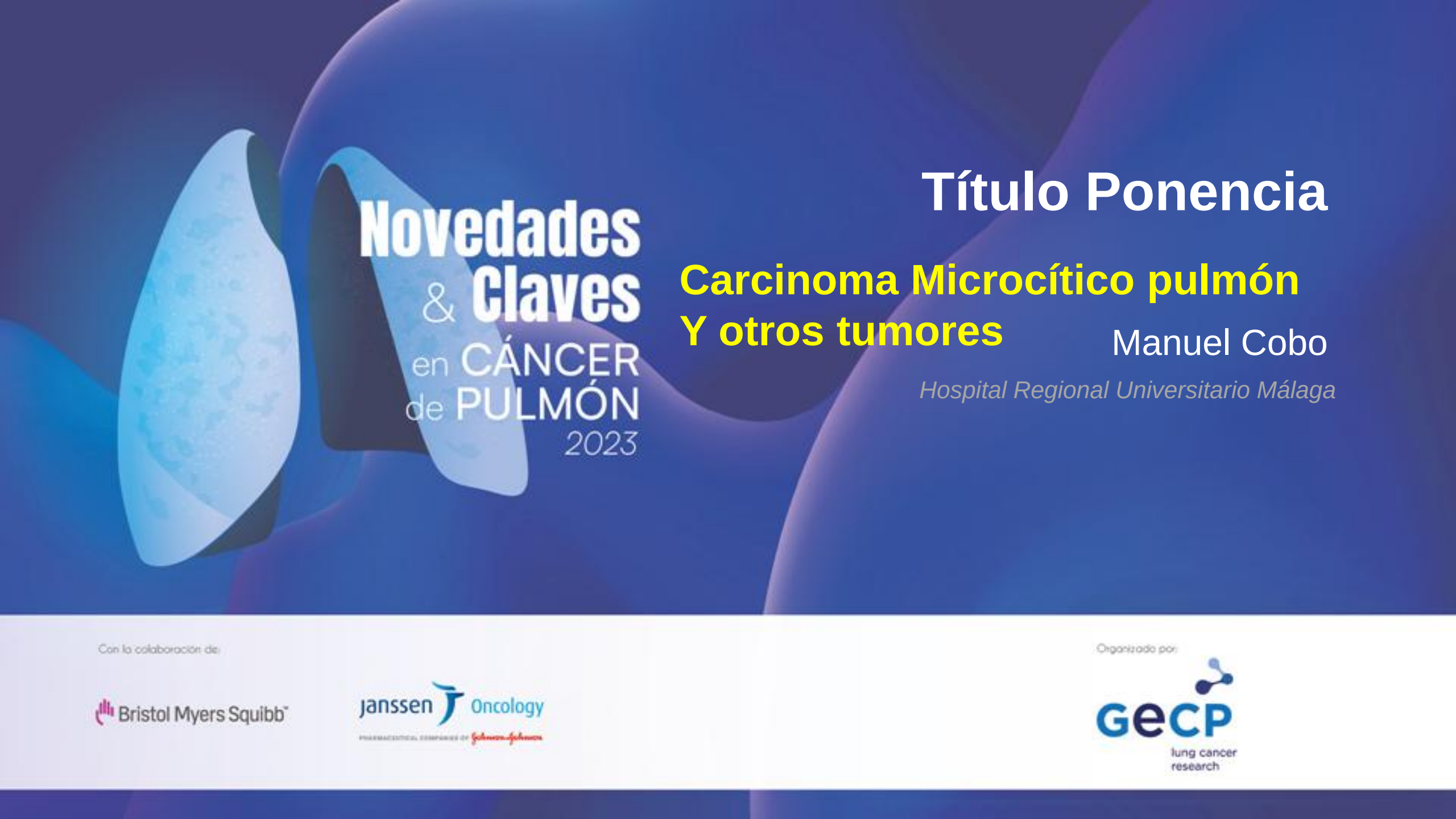


Título Ponencia

Carcinoma Microcítico pulmón
Y otros tumores

Manuel Cobo

Hospital Regional Universitario Málaga

Con la colaboración de:

Bristol Myers Squibb

janssen Oncology

Organizado por:

GECP lung cancer research

Small cell

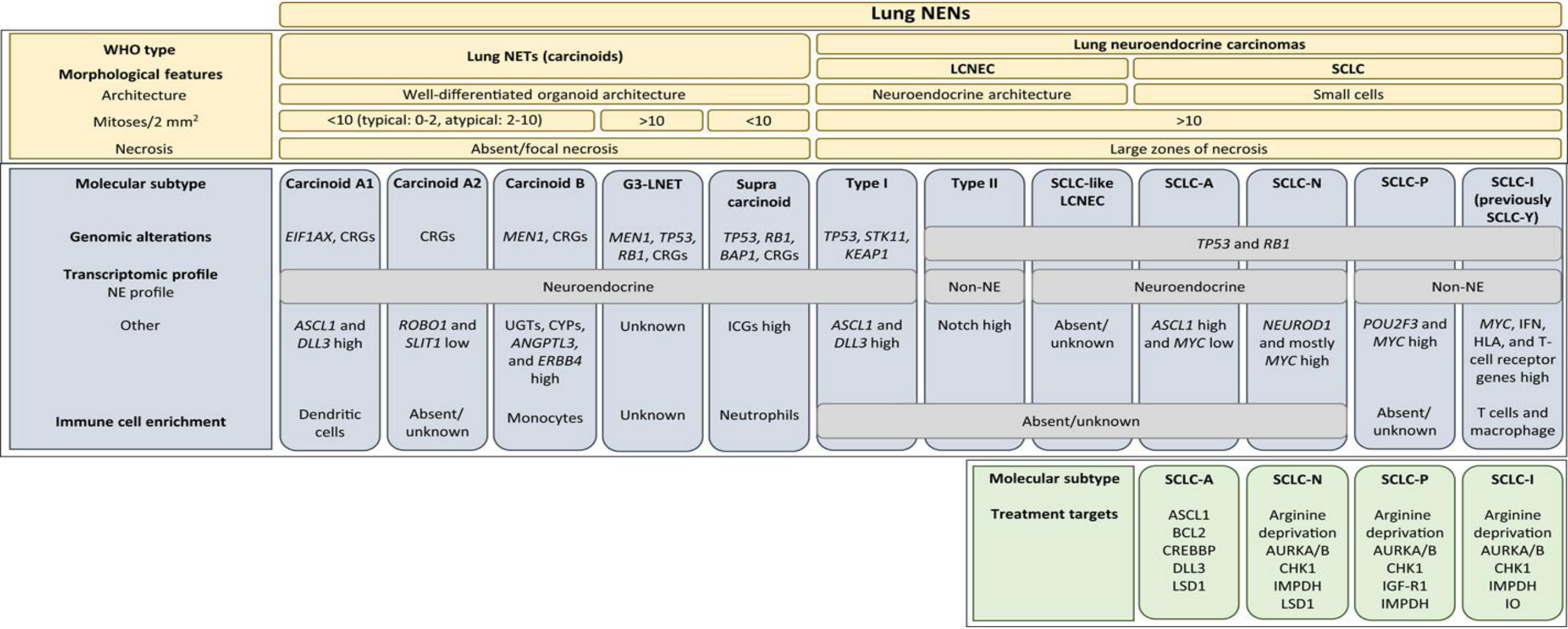
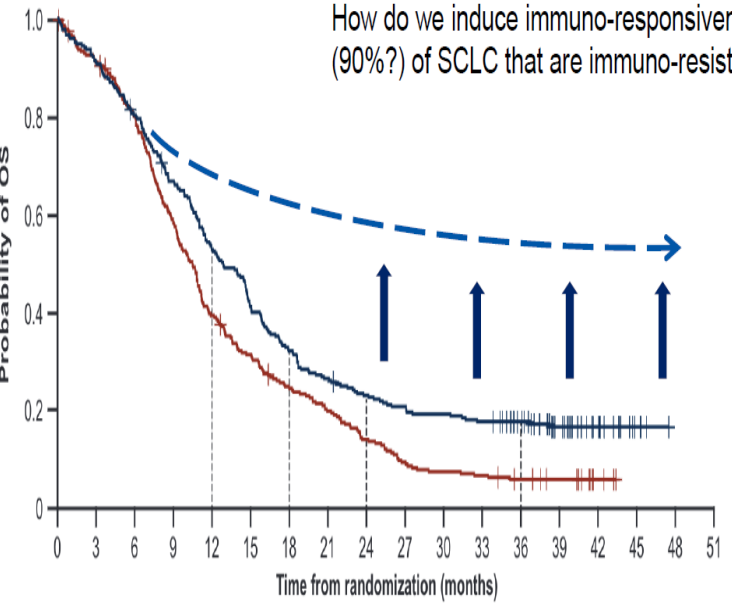


FIG 1. Morphological molecular spectrum of lung NENs. The current classification of lung NE neoplasms, subdivided into tumors (typical and atypical carcinoids) and carcinomas (LCNEC and SCLC) is depicted in orange. Diagnostic morphological features areas are described in the WHO Classification of Tumours.1 Molecular subtypes of each WHO type are described in blue, including characteristic genomic alterations and gene expression profiles, NE profile (on the basis of whole-transcriptome analyses or immunohistochemsistry of characteristic NE markers), and immune cell enrichment.6,10-13,16-20,43,46 Treatment targets for SCLC subtypes are depicted in teal.39 SCLC-I (previously SCLC-Y) may also be known as ASCL1/NEUROD1/POU2F3-negative SCLC. Note, G3-LNET (grade 3 lung NET), and supracarcinoids are emerging morphological and biological entities, respectively, with uncertain economic alterations because of low numbers; CRGs, chromatin remodeling genes; ICGs, immune checkpoint genes; IO, immuno-oncology; LCNEC, large-cell neuroendocrine carcinoma; NE, neuroendocrine; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumor; SCLC, small-cell lung carcinoma.

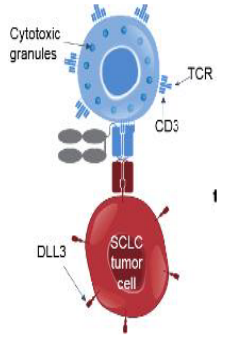
Published in: Lynnette Fernandez-Cuesta; Alexandra Sexton-Oates; Leyla Bayat; Matthieu Foll; Sally C.M. Lau; Ticiana Leal; *American Society of Clinical Oncology Educational Book* 2023 43e390794.
DOI: 10.1200/EDBK_390794



Some strategies to raise the tail of the survival curve for ES-SCLC

BiTEs?

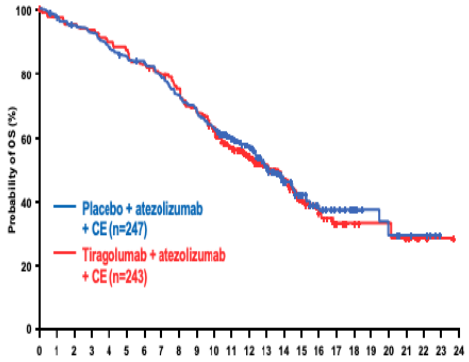
Tarlatamab? **MAYBE**



Paz-Ares et al., *J Thor Oncol* 2023

Synergy with other ICI?

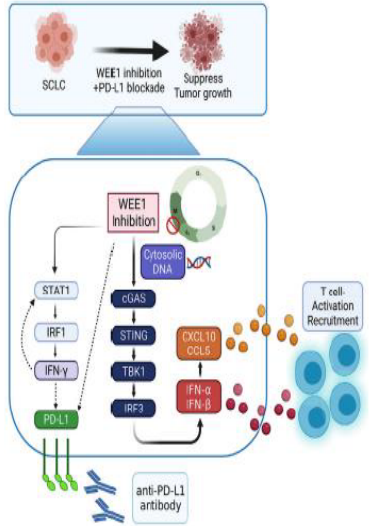
CTLA4? **NO** (CASPIAN)
TIGIT? **NO** (SKYSCRAPER2)



Paz-Ares et al., *ESMO Open* 2022
Rudin et al., *ASCO* 2022

DDRi to activate STING?

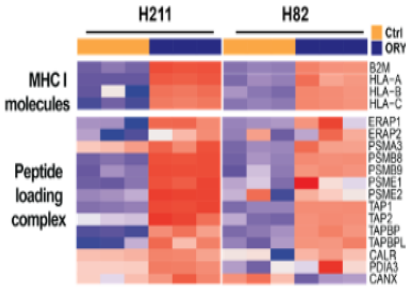
PARP? WEE1? **MAYBE**



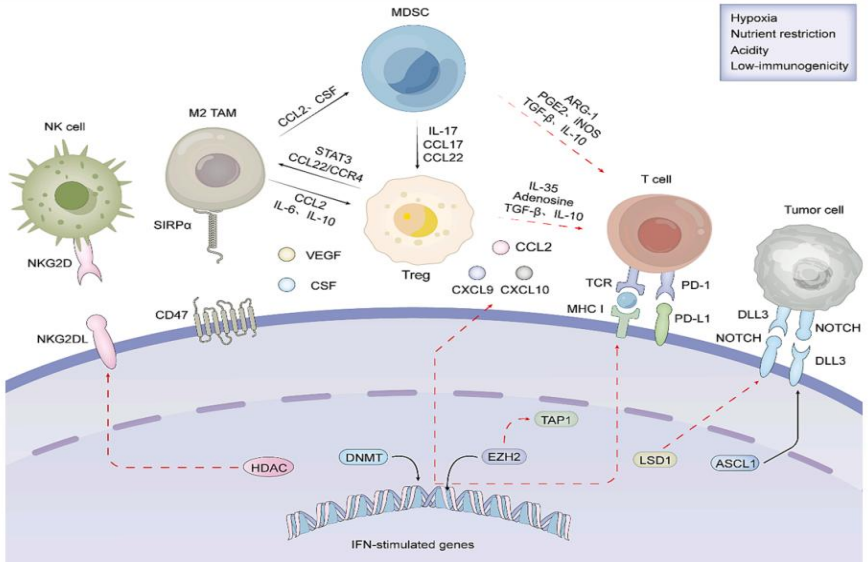
Sen et al., *Cancer Discov* 2019
Taniguchi et al., *Cell Rep* 2022

Epigenetic priming?

EZH2? LSD1? **MAYBE**



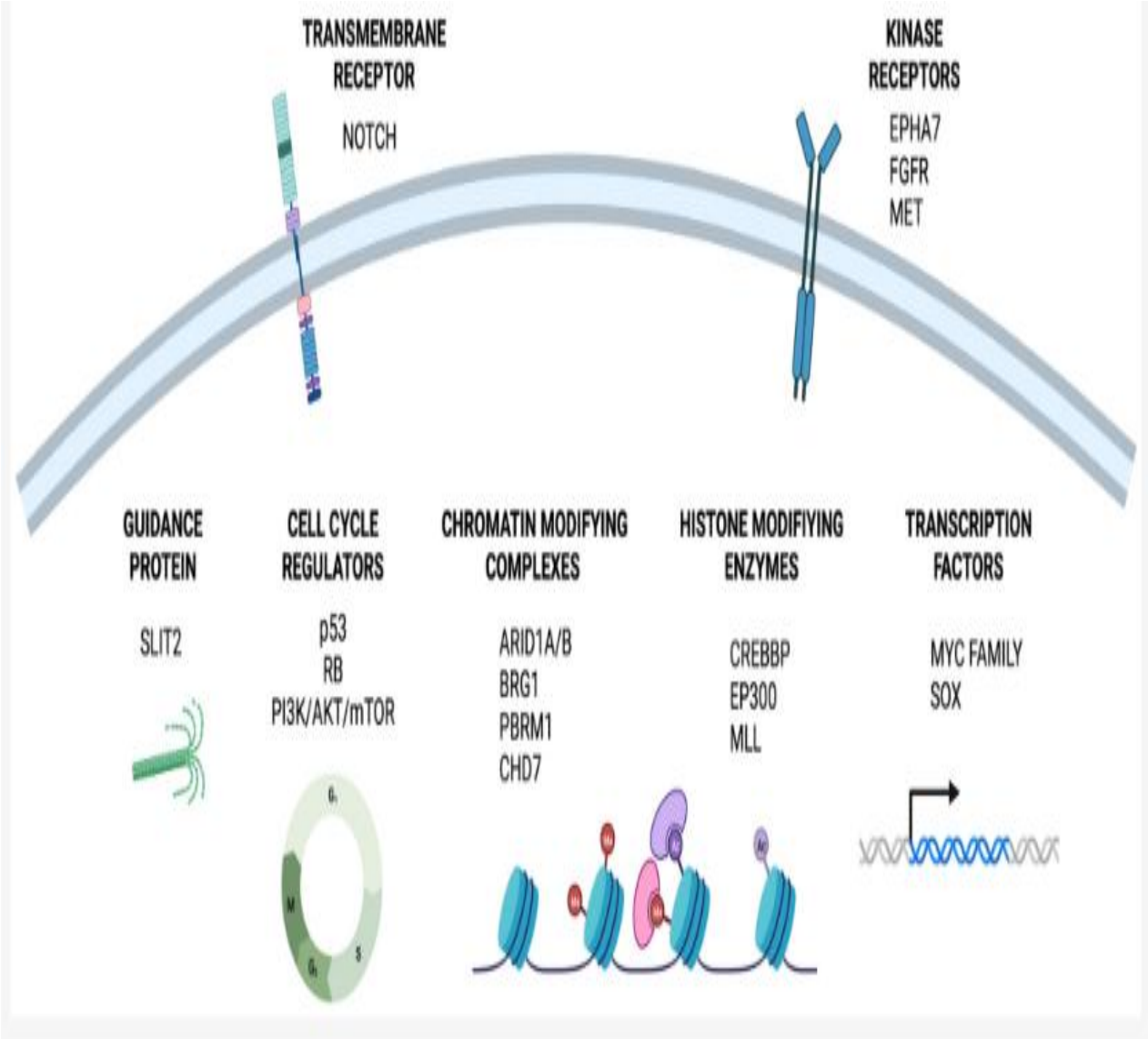
Mahadevan et al., *Cancer Discov* 2021
Nguyen et al., *J Thor Oncol* 2022
Hiatt et al., *Clin Cancer Res* 2022

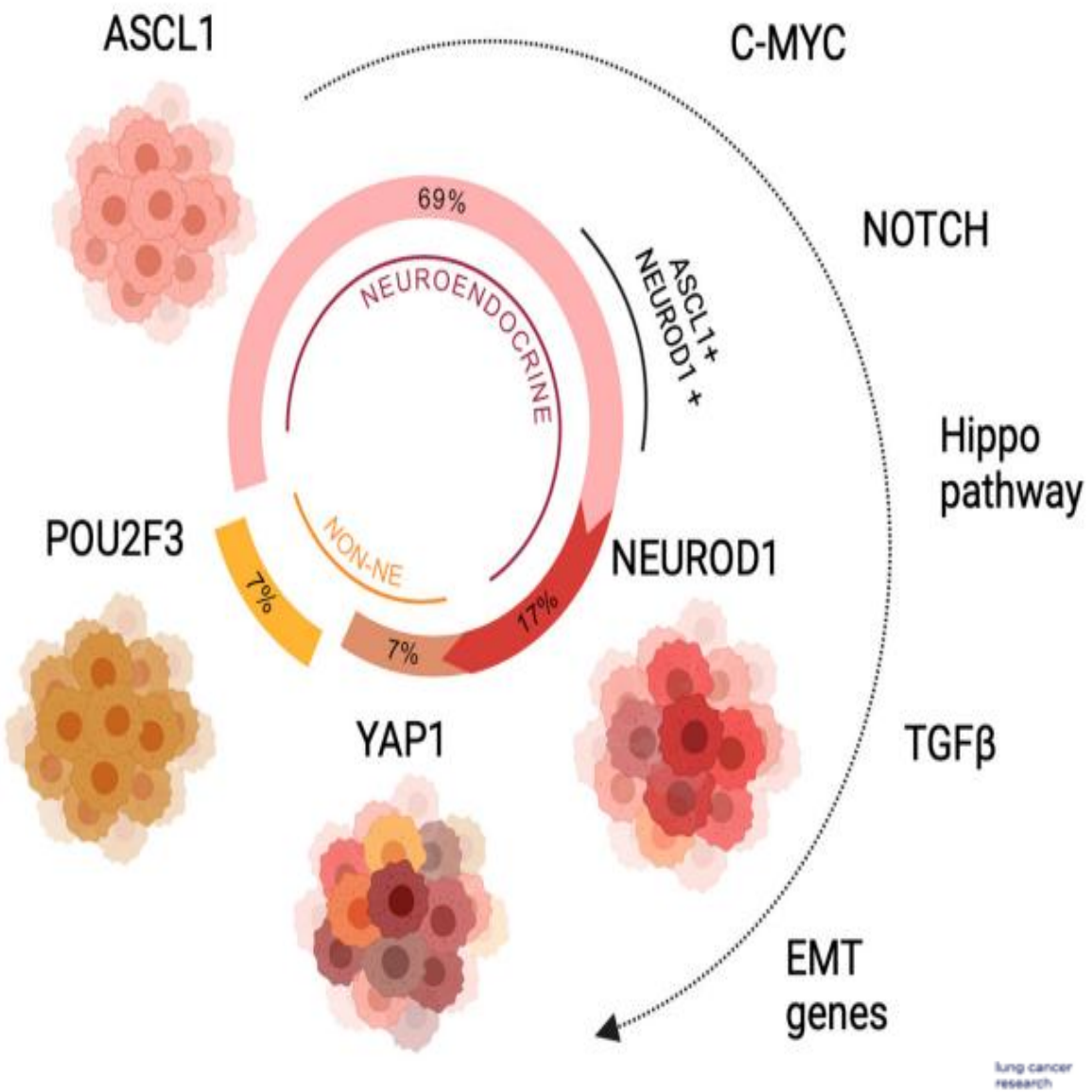


Mecanismos de formación de SCLC TIME. Los mecanismos epigenéticos afectan profundamente la inmunogenicidad del SCLC y reducen la quimiotaxis de las células T y la activación de las células NK. Mientras tanto, la hipoxia, la restricción de nutrientes y el ambiente metabólico ácido deterioran aún más la supervivencia de las células efectoras. Tregs generalizados concurrentes, M2Los TAM y MDSC en el microambiente forman una red inmunosupresora compleja que suprime de manera integral la función de las células T

Chen Y, Li H, Fan Y. Shaping the tumor immune microenvironment of SCLC: Mechanisms, and opportunities for immunotherapy. Cancer Treat Rev. 2023 Nov;120:102606

Representación de las alteraciones moleculares que juegan un papel en la progresión y recurrencia en SCLC





Gutiérrez M, Zamora I, Freeman MR, Encío IJ, Rotinen M. Actionable Driver Events in Small Cell Lung Cancer. Int J Mol Sci. 2023 Dec 20;25(1):105. doi: 10.3390/ijms25010105.

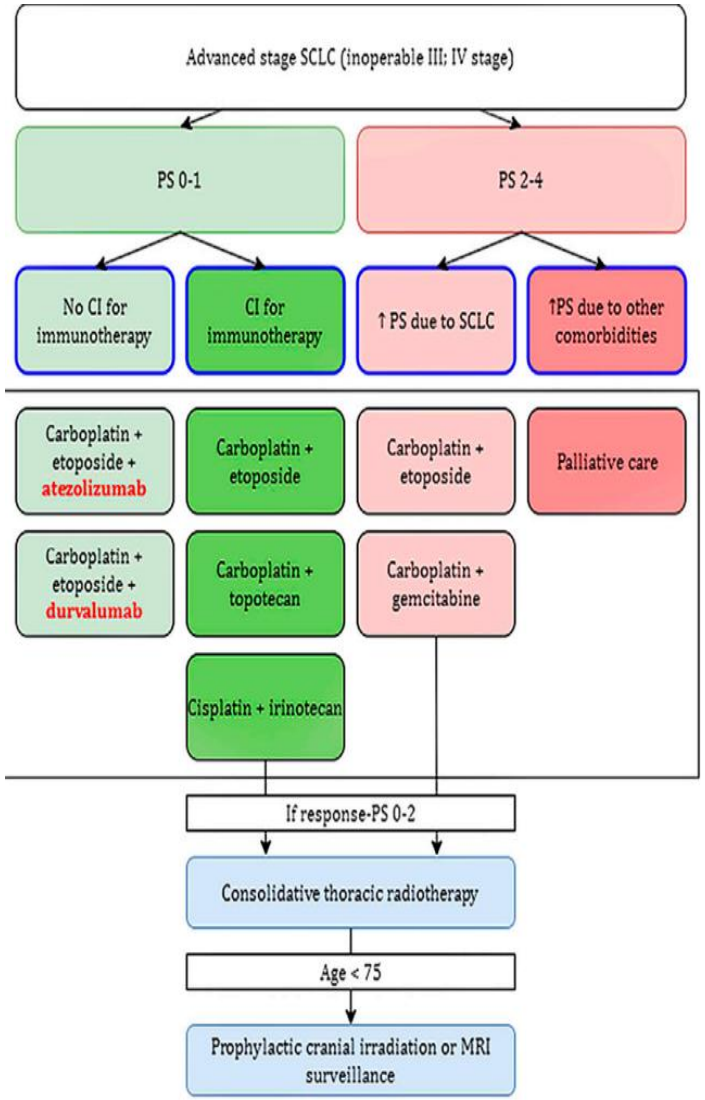
Adelantos y novedades presentes y futuras en SCLCC

.- Inmunoterapia

.- Target

.- Target + IO

.- ADCs



Skopelidou V,. Potential predictors of immunotherapy in small cell lung cancer. Pathol Oncol Res. 2023 May 3;29:1611086.

Adelantos y novedades presentes y futuras en SCLCC

.- Inmunoterapia

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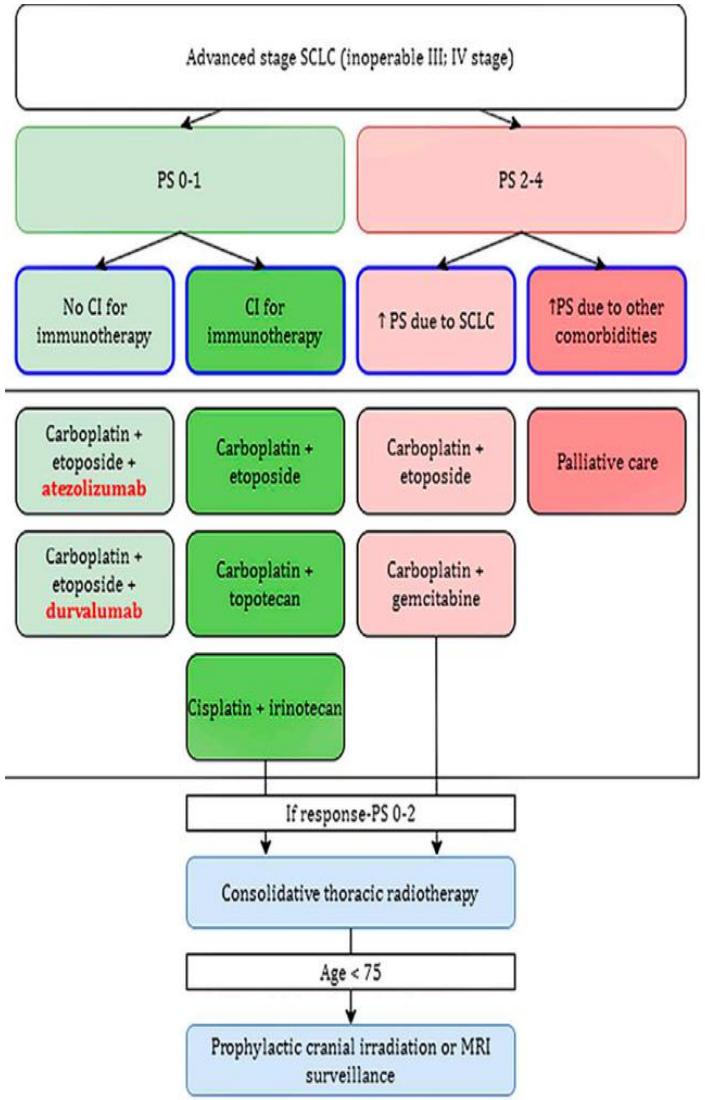


Skopelidou V,. Potential predictors of immunotherapy in small cell lung cancer. Pathol Oncol Res. 2023 May 3;29:1611086.

IASLC | 2023 World Conference on Lung Cancer
SEPTEMBER 9-12, 2023 | SINGAPORE

First-line Chemotherapy With or Without Tislelizumab for Extensive-stage Small Cell Lung Cancer: RATIONALE-312 Phase 3 Study

Ying Cheng,[1*] Yun Fan,[2] Yanqiu Zhao,[3] Dingzhi Huang,[4] Xingya Li,[5] Peng Zhang,[6] Mafei Kang,[7] Nong Yang,[8] Diansheng Zhong,[9] Zhen Wang,[10] Yan Yu,[11] Yu Zhang,[12] Jun Zhao,[13] Tai Qin,[14] Chenqi Chen,[15] Shiangjiin Leaw,[15] Wenjuan Zheng,[14] and Yong Song,[16] on behalf of the RATIONALE-312 Study Group

Study Design

Randomized, double-blind, placebo-controlled, multicenter, phase 3 study (NCT04005716)

Key eligibility criteria
- Patients aged ≥18 years with histologically/cytologically confirmed ES-SCLC
- No prior systemic treatment for ES-SCLC
- ECOG PS ≤1

R 1:1

Induction treatment (Q3W, four cycles)
- Tislelizumab 200 mg D1 + carboplatin (AUC 5) or cisplatin (75 mg/m²), D1 + etoposide (100 mg/m²), D1-3
- Placebo D1 + carboplatin (AUC 5) or cisplatin (75 mg/m²), D1 + etoposide (100 mg/m²), D1-3

Maintenance treatment
- Tislelizumab 200 mg Q3W
- Placebo Q3W

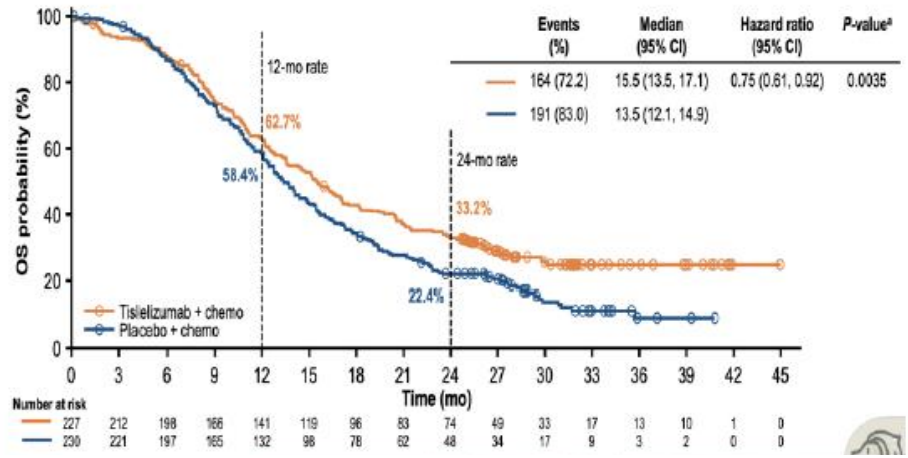
Continue until disease progression or intolerable toxicity

Stratification factors
- ECOG PS (0 vs 1)
- Cisplatin vs carboplatin
- Brain metastasis (yes vs no)

Primary endpoint: OS
Key secondary endpoints:
- PFS, ORR, and DoR (INV-assessed)
- Safety and tolerability

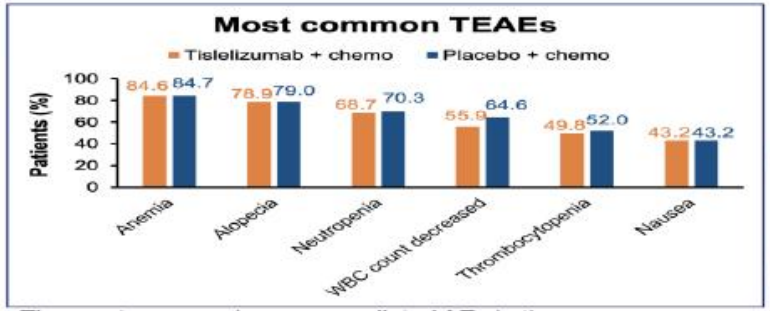
Statistical methods
- Planned to enroll 455 pts; 80% power to detect HR 0.74 with 353 OS events
- Hierarchical testing on PFS: only when OS demonstrates significance[a]

Overall Survival (OS)



Safety Summary

	Tislelizumab + chemo (n=227)	Placebo + chemo (n=229)
Tislelizumab/placebo cycles		
Mean	11.8	7.3
Median (range)	6.0 (1-59)	6.0 (1-48)
>16 cycles, n (%)	44 (19.4%)	10 (4.4%)
Chemotherapy cycles, median, n (range)	4 (1-4)	4 (1-4)
TEAEs, n (%)	226 (99.6)	228 (99.6)
Treatment-related[a]	226 (99.6)	228 (99.6)
Grade ≥3	201 (88.5)	206 (90.0)
Serious	94 (41.4)	69 (30.1)
Leading to discontinuation[b]	30 (13.2)	7 (3.1)
Leading to death[c]	14 (6.2)	4 (1.7)
Tislelizumab/placebo-related	7 (3.1)	0 (0.0)
Chemotherapy-related	6 (2.6)	0 (0.0)
Immune-mediated AEs, n (%)	87 (38.3)	41 (17.9)
Leading to death	1 (0.4)	0 (0.0)
Infusion-related reactions, n (%)	8 (3.5)	5 (2.2)



The most common immune-mediated AEs in the tislelizumab plus chemo arm were hypothyroidism (13.7%), rash (13.2%), hyperthyroidism (5.7%)

MADRID 2023 ESMO congress

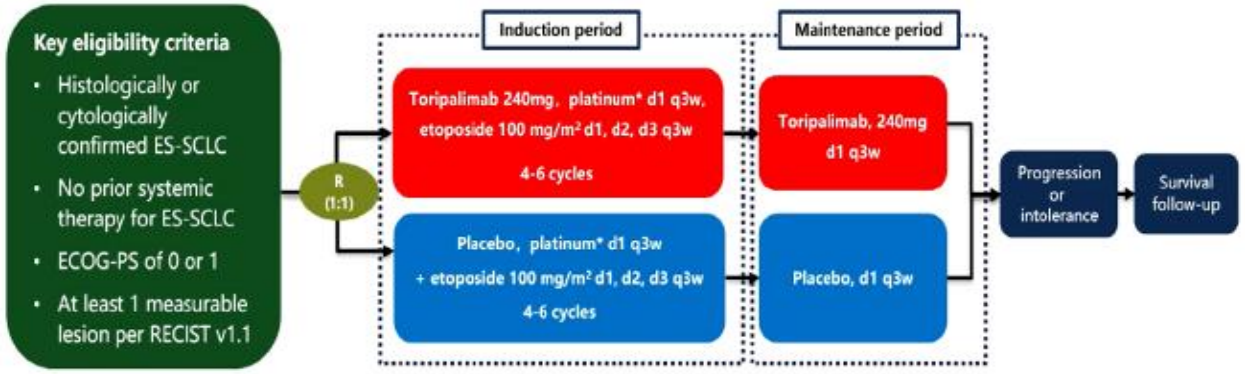
EXTENTORCH: A Randomized, Phase III Trial of Toripalimab Versus Placebo, in Combination with Chemotherapy as a First-line Therapy for Patients with Extensive Stage Small Cell Lung Cancer

Y. Cheng[1,*], Y. Liu[2], W. Zhang[3], L. Wu[4], C. Zhou[5], D. Wang[6], B. Xia[7], M. Bi[8], X. Fu[9], C. Li[10], G. Chen[11], D. Lv[12], Y. Zhao[13], J. Huang[14], M. Li[15], T. Yi[16], X. Huang[17], R. Yang[18], Z. Chen[19,*], Y. Wang[20]

[1] Medical oncology, Jilin Cancer Hospital, Changchun, China; [2] Medical oncology, Jilin Cancer Hospital, Changchun, China; [3] Respiratory medicine department, The First Affiliated Hospital of Nanchang University, Nanchang, China; [4] Thoracic Medical Oncology Department, Hunan Cancer Hospital, Changsha, China; [5] Department of Medical Oncology, Shanghai Pulmonary Hospital, Shanghai, China; [6] Medical oncology, Chongqing Cancer Hospital, Chongqing, China; [7] Thoracic Oncology, Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine, Hangzhou, China; [8] Medical oncology, The First Affiliated Hospital of Bengbu Medical College, Bengbu, China; [9] Respiratory medicine department, The Affiliated Hospital of Inner Mongolia Medical University, Hohhot, China; [10] Respiratory medicine department, The Third Affiliated Hospital of Soochow University (The First People's Hospital of Changzhou), Changzhou, China; [11] Medical oncology, Cancer Hospital Affiliated to Harbin Medical University, Harbin, China; [12] Respiratory medicine department, Affiliated Taizhou Hospital of Zhejiang Province of Wenzhou Medical University, Taizhou, China; [13] Respiratory medicine department, Henan Cancer Hospital/Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, China; [14] Department of Respiration, The First Affiliated Hospital Of Soochow University, Suzhou, China; [15] Respiratory medicine department, Xiangya Hospital of Central South University, Changsha, China; [16] Medical oncology, Xiangyang Central Hospital, Xiangyang, China; [17] Medical oncology, Chongqing University Three Gorges Hospital, Chongqing, China; [18] Medical oncology, Yunnan Cancer Hospital & The Third Affiliated Hospital of Kunming Medical University & Yunnan Cancer Center, Kunming, China; [19] Medical oncology, The Second Affiliated Hospital of Anhui Medical University, Hefei, China; [20] Department of Respiratory and Critical Care Medicine, West China School of Medicine/West China Hospital of Sichuan University, Chengdu, China

*Corresponding Author

Presented by Y. Liu on behalf of the EXTENTORCH investigators at Madrid, Spain, 21 Oct 2023



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

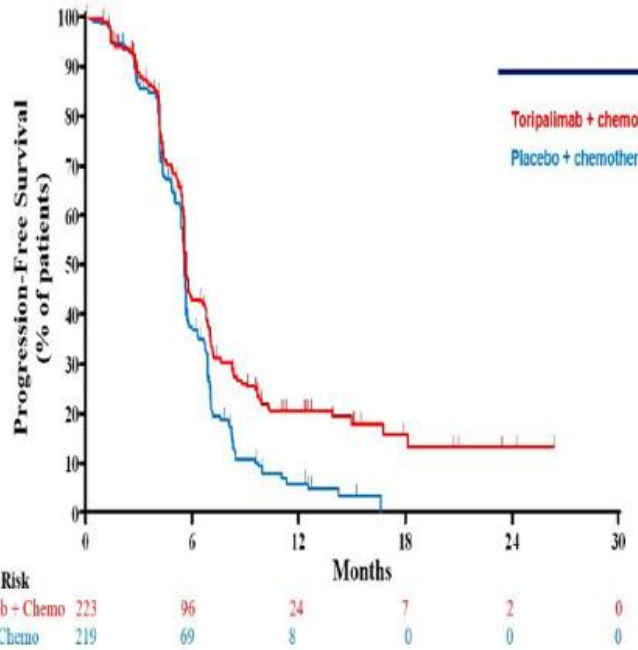
Primary endpoint: PFS by investigator per RECIST v1.1 and OS

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.

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

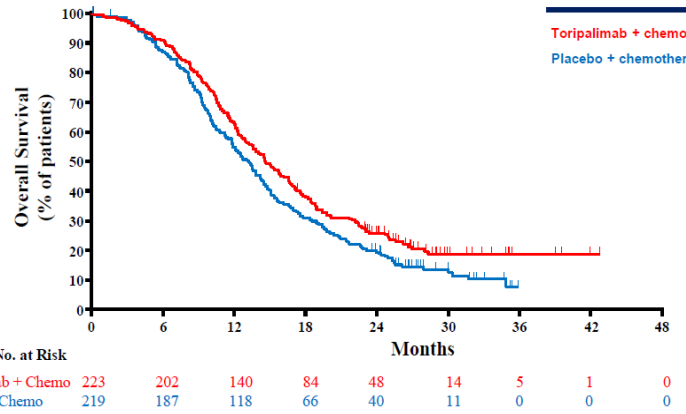


	No. of events/total No. of patients	Median PFS, months (95% CI)	1-Yr PFS rate, % (95% CI)
Toripalimab + chemotherapy	171/223	5.8 (5.6, 6.8)	18.1 (12.9, 24.0)
Placebo + chemotherapy	190/219	5.6 (5.5, 5.7)	4.9 (2.4, 8.8)

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

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)

* Tyrosine Kinase Inhibitor included Anlotinib and Osimertinib, etc.

MADRID ESMO congress

Ying Liu, et al. ESMO 2023

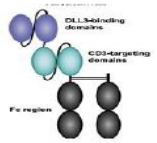
	Impower 133 Atezolizumab (ant- PD-L1)	CASPIAN Durvalumab (anti-PD-L1)	Capstone-1 Adebrelimab (anti PD-L1)	KN604 Pembrolizumab (anti- PD-1)	ASTRUM-005 Serplulimab (anti-PD-1)	RATIONALE -312 Tislelizumab (anti- PD-1)	EXTENTORCH Toripalimab (anti-PD-1)
N	403	805	462	453	585	457	442
mSG QT-IO/QT-Pcb HR (95% 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

Courtesy Manuel Dómine

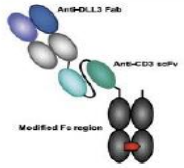
DLL3/CD3 TARGETED THERAPIES: T-CELL ENGAGERS

Tarlatamab
Bispecific mAb (BiTE®)
Amgen
(Phase 2-3)

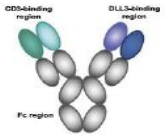


Fc domain
(to extend half-life)

QLS31904
Bispecific mAb
Qilu Pharmaceuticals
(Phase 1)

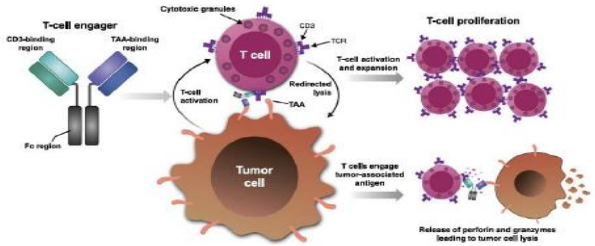


BI 764532[2]
Bispecific mAb
Boehringer Ingelheim
(FIH)

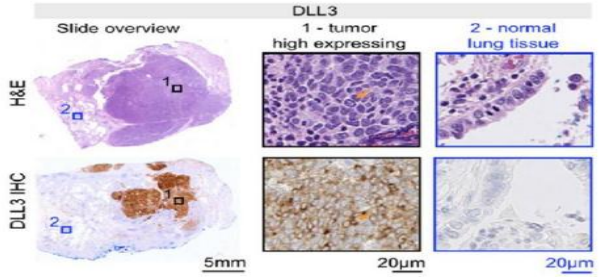


IgG-like
structure

HPN328
Trispecific mAb (TriTAC®)
Harpoon Therapeutics
(Phase 1/2)

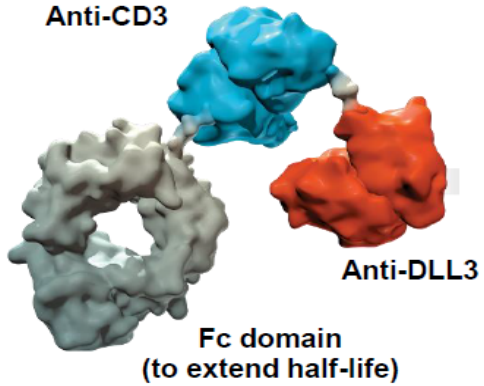


DLL3 is highly upregulated and expressed on the surface of SCLC tumour cel
(80% RNA and protein) and other neuroendocrine tumours[3,4]



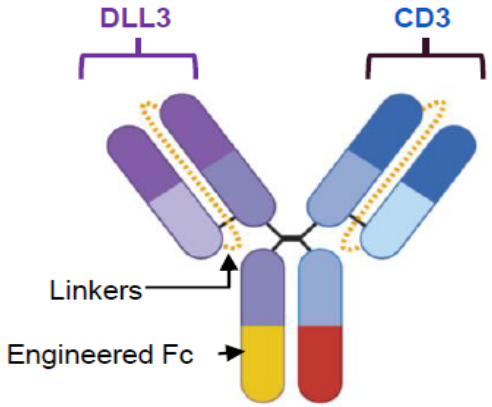
1.-Rudin C, et al. J Hematol Oncol 2023; 2.- Wermke M et al. ASCO 2023; 3.- Sabari JK, et al. Nat Rev Clin Oncol 2017; 4.-Owen DH, et al. J Hematol Oncol 2019

Tarlatamab
Half-life extended BiTE® molecule
(bispecific T-cell engager)
Phase 2/3, Amgen[1,2]



HPN328
TriTAC® (trispecific
T cell-activating construct)
Phase 1/2, Harpoon
Therapeutics[3,4]

BI 764532
Bispecific mAb
Phase 1/2, Boehringer Ingelheim



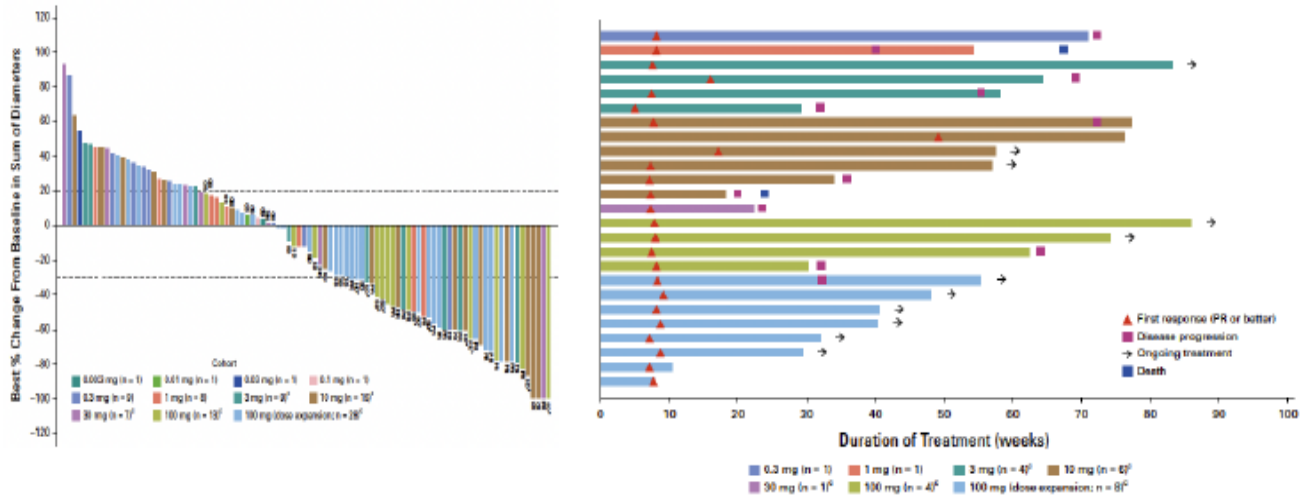
Organizado por
GECP
lung cancer research

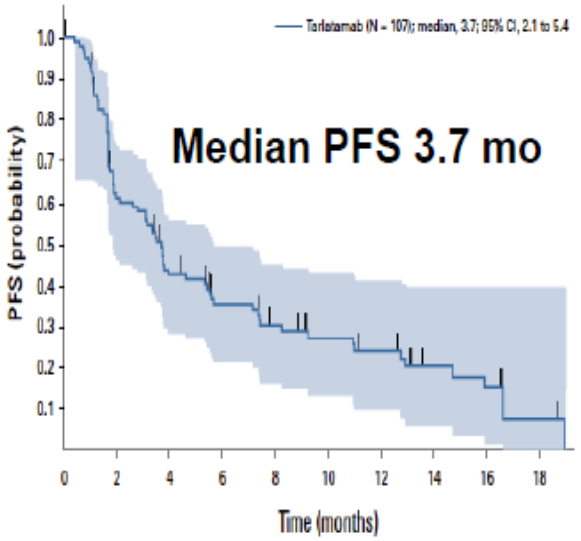
Tarlatamab (AMG 757). Recurrent SCLC. /DeLLp1-300

Modified RECIST 1.1 Response	Patients* (N = 105) n (%)
ORR, n (%)	
Confirmed and unconfirmed	29 (28)
Confirmed	**24 (23)**
Disease control rate, n (%)	55 (52)
Best overall response, n (%)	
Confirmed CR	2 (2)
Confirmed PR	22 (21)
SD	31 (30)
PD	8 (8)
Could not be evaluated†	35 (33)
Unconfirmed PD†	33 (31)
No assessment‡	7 (7)

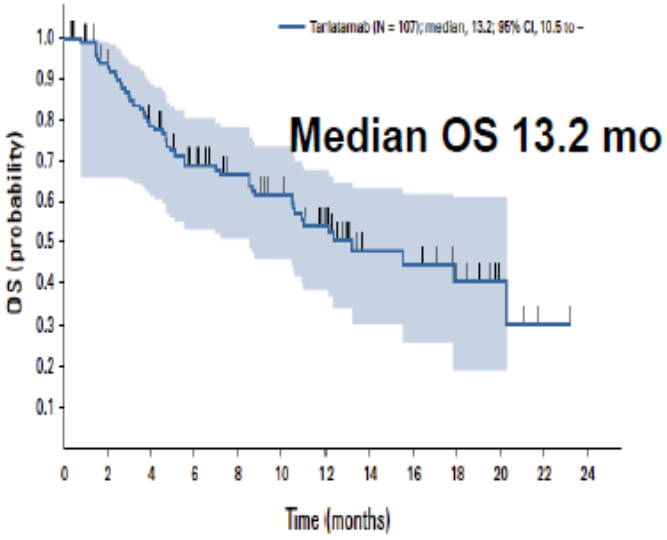
Median time to response 1.8 months

Median DoR 12.3 mo





Median PFS 3.7 mo

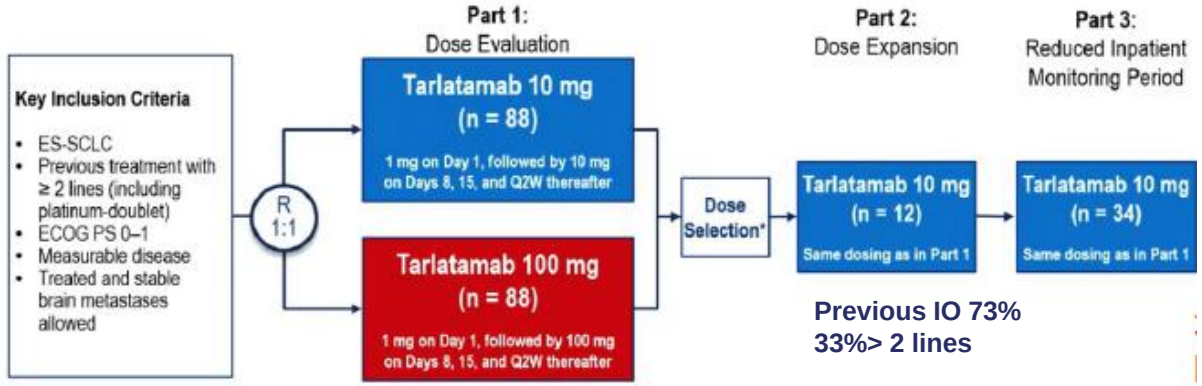


Median OS 13.2 mo

Paz-Ares,et al. JCO 2023

DeLLphi-301 Study Design

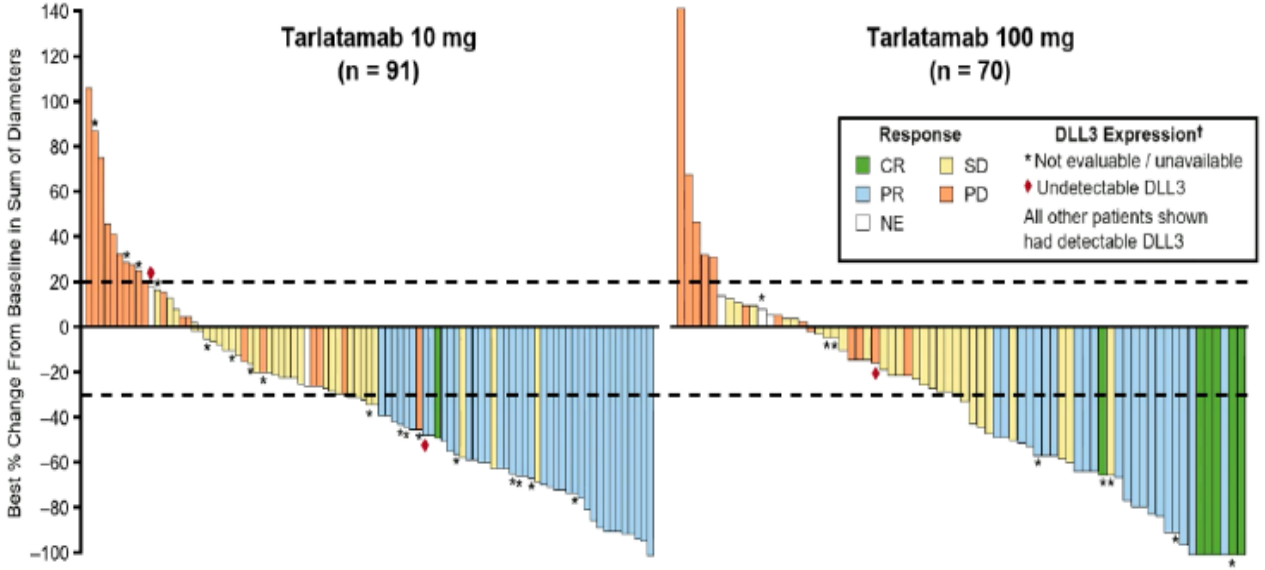
Phase 2, open-label study (NCT05060016)



Previous IO 73%
33%> 2 lines

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

Anti-tumor Activity



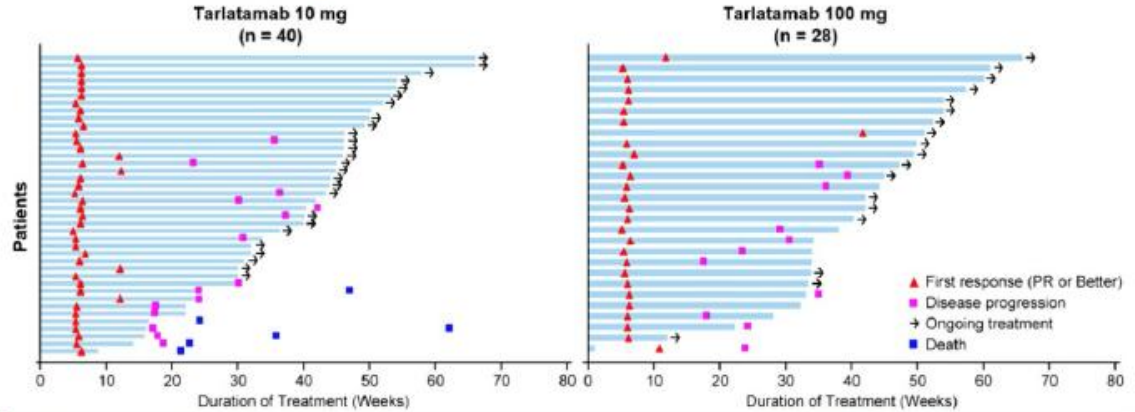
Responses were observed regardless of DLL3 expression, as well as in patients without evaluable tumor tissue

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%

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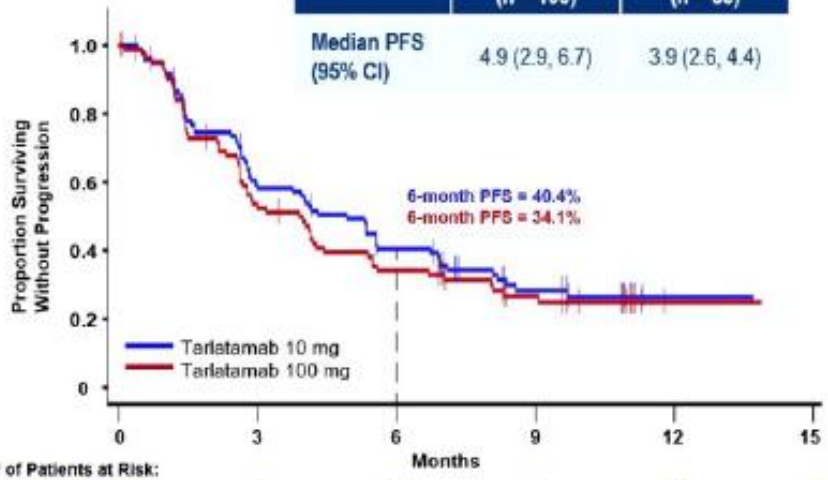
Median follow-up time for DOR, 9.5 months (95% CI: 8.3, 9.7 months).
DOR, duration of response; PR, partial response; TTR, time to objective response.

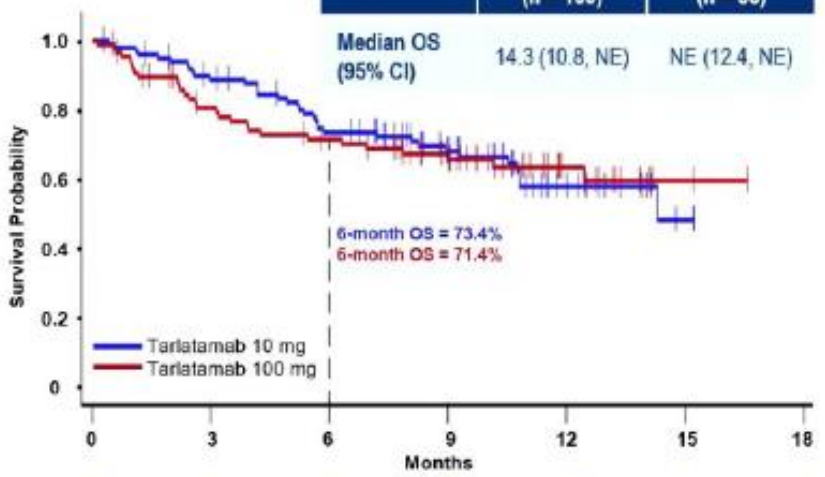
Outcome	Tarlatamab 10 mg (n = 100)	Tarlatamab 100 mg (n = 88)
Median PFS (95% CI)	4.9 (2.9, 6.7)	3.9 (2.6, 4.4)



Number of Patients at Risk:

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

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



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

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

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.

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)

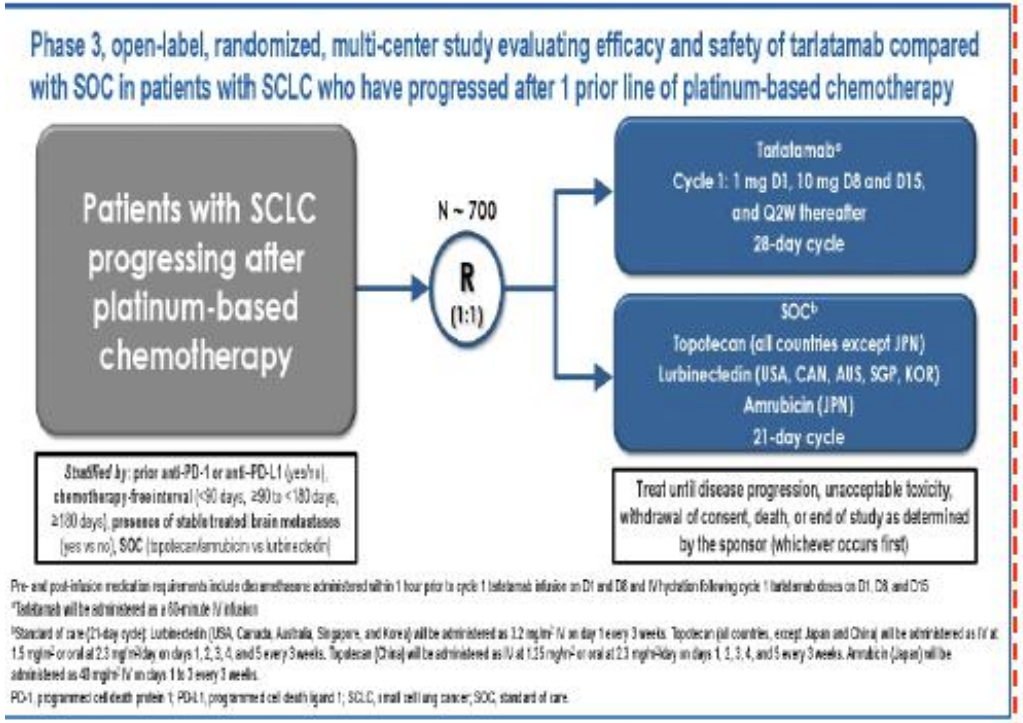
Organizado por: GECP lung cancer research

Paz-Ares L. ESMO 2023. Myung-Ju Anh. NELM 2023

DeLLphi-304

Phase 3 AMG 757 in 2L

Tartalamab vs SoC[2]

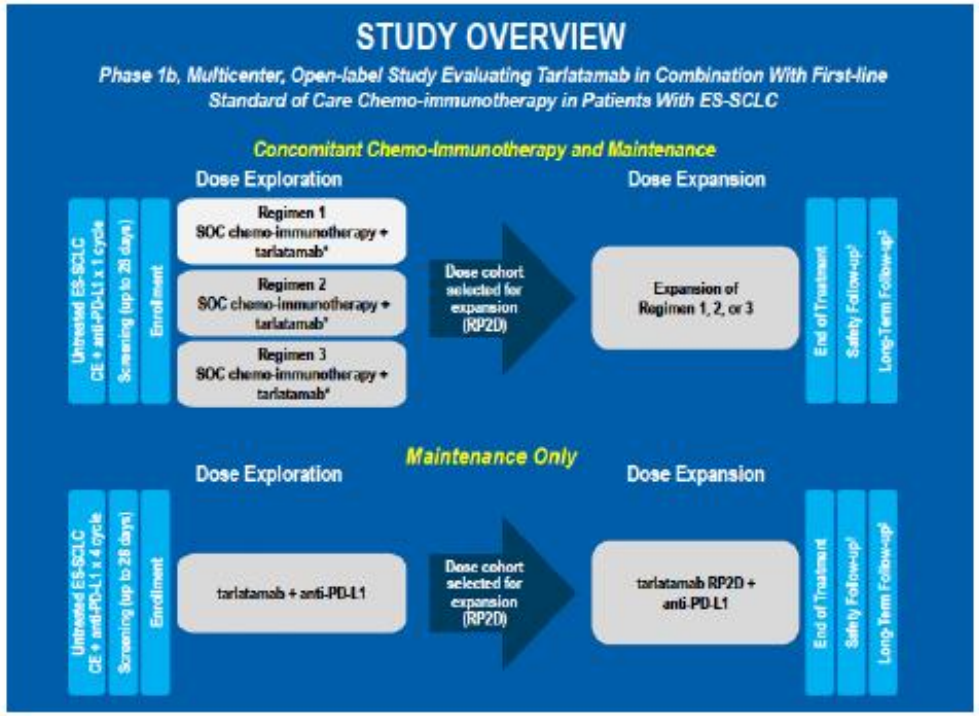


NCT05740566, ongoing

DeLLphi-303

Phase 1b AMG 757 in 1L

Chemo-IO-T-> maintenance IO-T[3]



NCT05361395, ongoing

Organizado por

GECP lung cancer research

BI 764532. Pts wit SCLC or NECs (NCT04429087)

ECOG 0-1 and DLL3-positive required for inclusion

OVERALL COHORT*	N=107†
Median age, years (range)	60.0 (32–79)
Male, n (%)	61 (57)
Prior lines of therapy, n (%)	
1–2	72 (67)
≥3	33 (31)
ECOG PS 0/1, n (%)	28 (26)/78 (73)
Prior PD-1/PD-L1, n (%)	52 (49)
Brain/liver metastases, n (%)	41 (38)/60 (56)

†Safety population: ≥1 dose of BI 764532
* As of March 26 2023

RESULTS IN THE COHORT OF SCLC (n=57) and LCNEC (n=9)

Primary endpoint: SAFETY (MDT/DLT)

DLTs (CRS G3-4, confusional state G3, infusion reaction G2, nervous system disorder G3), were **reversible.**

Low discontinuation rate 6%

CRS most common AE (48%, mostly G1–2)

Lymphocyte count decrease most common G3 AE (18%)

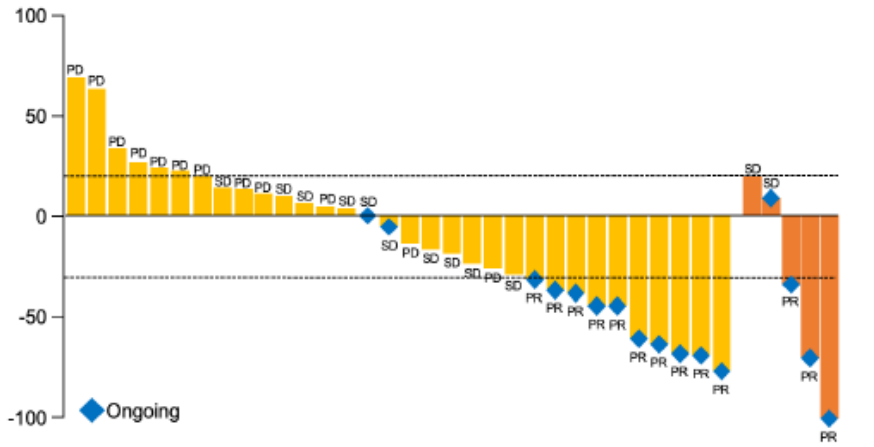
Secondary endpoint: EFICACY (ORR), N=44

Efficacy observed at doses **≥ 90 µg/kg**

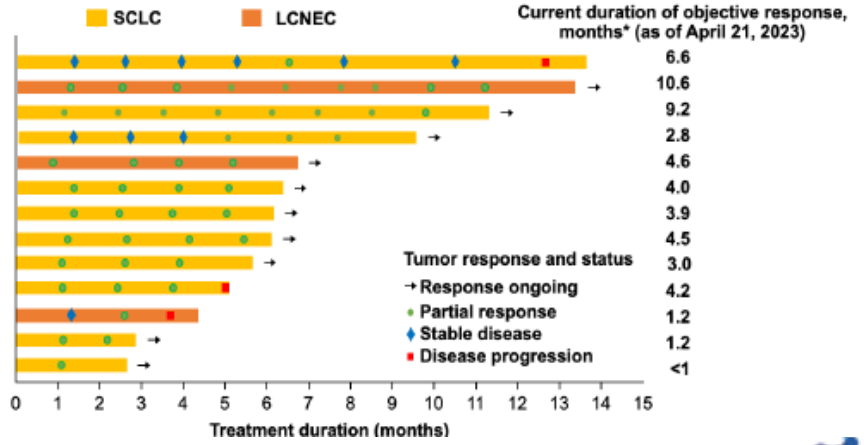
ORR (at doses ≥ 90 µg/kg): **SCLC 26%, LCNEC 60%**

Durable responses the majority ongoing (10/13)

Efficacy in patients with SCLC and LCNEC (doses ≥ 90µg/kg)



Response duration in patients with SCLC and LCNEC



GECP lung cancer research

Wemke M. et al. ASCO 2023. / IASLC 2023

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, ICO 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/m²	7% 2 prior L	II	105	35	5.3	3.5	9.3
Lurbinectidin + Doxo Vs control arm (Atlantis) *Pozo S, Lancet Respir Med 2023*	2 + 40 mg/m²	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

Courtesy Manuel Dómine

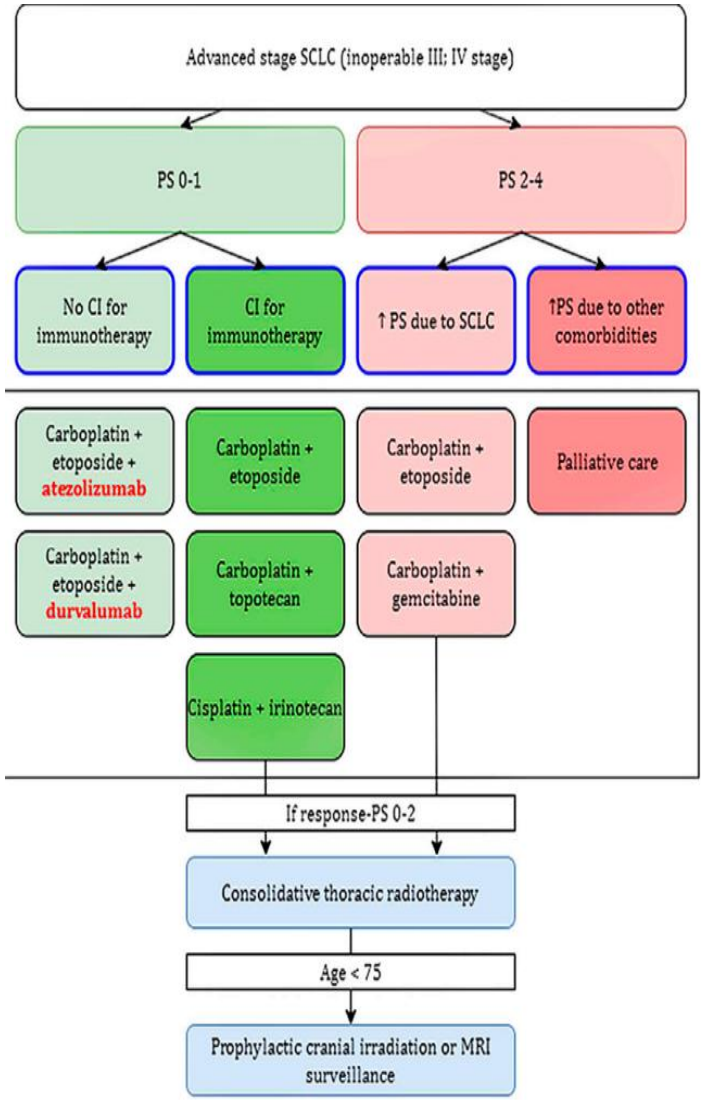
Adelantos y novedades presentes y futuras en SCLCC

.- Inmunoterapia

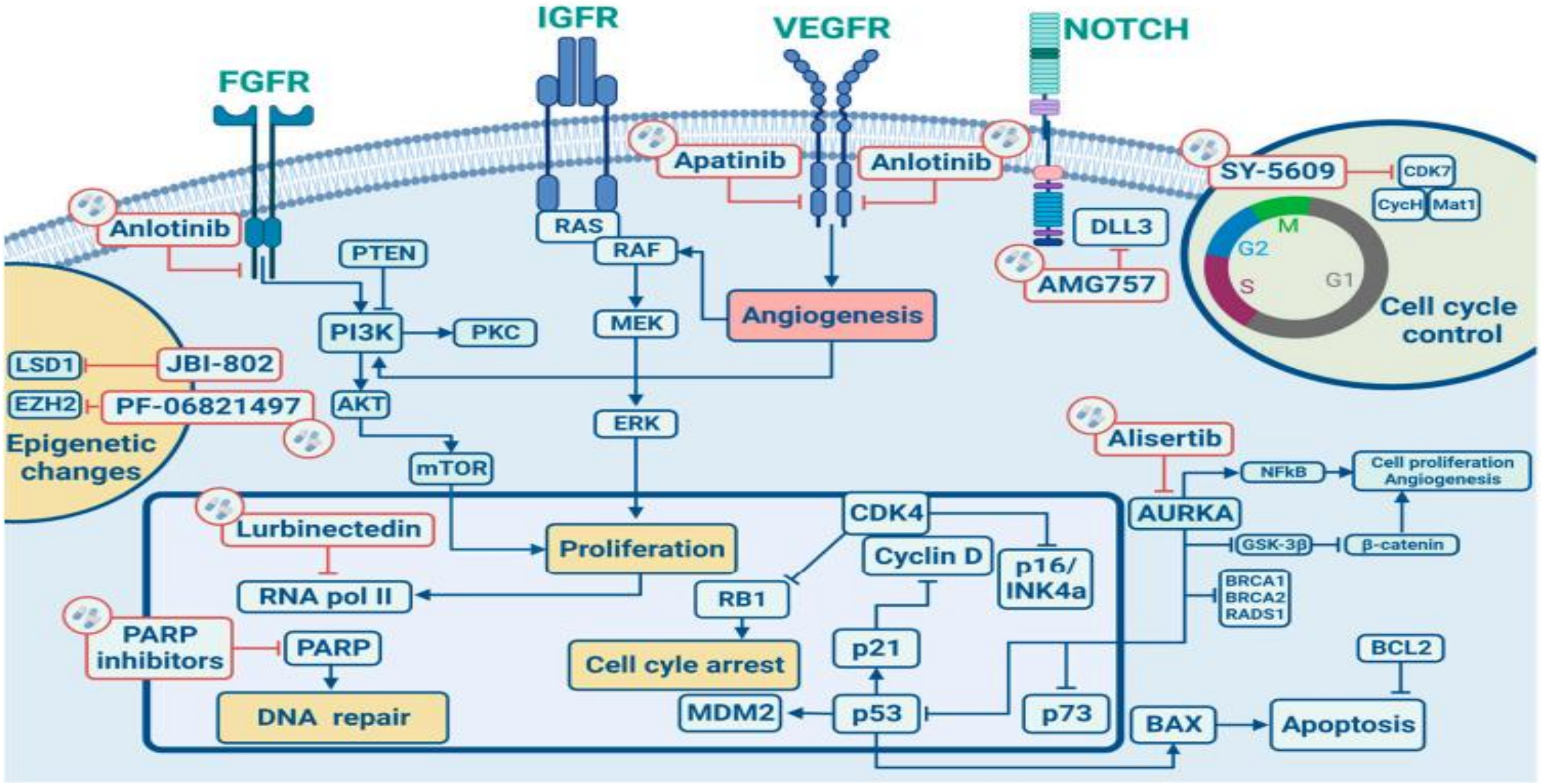
.- Target

.- Target + IO

.- ADCs

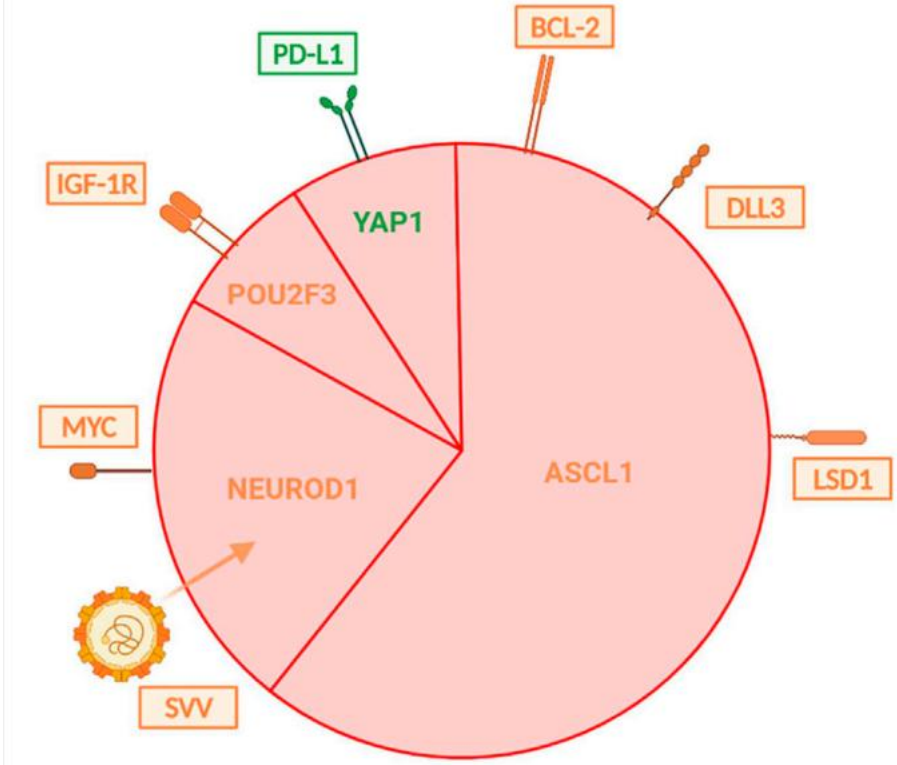


Skopelidou V,. Potential predictors of immunotherapy in small cell lung cancer. Pathol Oncol Res. 2023 May 3;29:1611086.



Cani M, etal. Targeted Therapies in Small Cell Lung Cancer: From Old Failures to Novel Therapeutic Strategies. Int J Mol Sci. 2023 May 17;24(10):8883

Molecular subtype	SCLC-A	SCLC-N	SCLC-P	SCLC-I
Definitive transcription factor	ASCL1	NEUROD1	POU2F3	
Phenotype	NE		non-NE	
	classical NE high	variant NE low		
Mutation	TP53 & RB1 inactivation			
Marker expression	CHGA SYP SOX2 MYCL DLL3 BCL-2 LSD SLFN11 INSM1 TTF-1	CHGA SYP MYC AURK INSM1	REST NOTCH IGF1R EMT	REST NOTCH BTK EMT
Potential therapeutics	PARP inhibitor DLL3 targeted therapy BCL-2 inhibitor LSD inhibitor	AURK inhibitor CHK1 inhibitor	PARP inhibitor IGF1R inhibitor	ICI BTK inhibitor



SCLC-A	SCLC-N	SCLC-P	SCLC-I
ASCL1 BCL2 CREBBP DLL3 LSD1	Arginine deprivation AURKA/B CHK1 IMPDH LSD1	Arginine deprivation AURKA/B CHK1 IGF-R1 IMPDH	Arginine deprivation AURKA/B CHK1 IMPDH IO

Skopelidou V,. Potential predictors of immunotherapy in small cell lung cancer. Pathol Oncol Res. 2023 May 3;29:1611086.

Saida Y, et al. Extensive-Stage Small-Cell Lung Cancer: Current Landscape and Future Prospects. Onco Targets Ther. 2023 Aug 2;16:657-671.

elcc European Lung Cancer Congress 2023

RESILIENT Part 2: A Randomized, Open-label Phase 3 Study of Liposomal Irinotecan versus Topotecan in Adults with Relapsed SCLC

Charles M. Rudin,[1] Afshin Dowlati,[2] Yuanbin Chen,[3] Alejandro Navarro,[4] James Chih-Hsin Yang,[5] Goran Stojanovic,[6] Patricia Rich,[7] Zoran G. Andric,[8] Yi-Long Wu,[9] Huanyu Chen,[10] Li Zhang,[10] Stanley Yeung,[10] Fawzi Benzaghou,[10] Luis Paz-Ares,[11] Paul A. Bunn[12]

[1]Druckenmiller Center for Lung Cancer Research, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]University Hospitals Seidman Cancer Center and Case Western Reserve University, Cleveland, OH, USA; [3]Cancer and Hematology Centers of Western Michigan, Grand Rapids, MI, USA; [4]Hospital Universitario Vall d'Hebron and Vall d'Hebron Institute of Oncology, Barcelona, Spain; [5]National Taiwan University Hospital and National Taiwan University Cancer Center, Taipei, Taiwan; [6]Institute for Pulmonary Diseases of Vojvodina, Sremska Kamenica, Serbia; [7]Southeastern Regional Medical Center, Lumberton, NC, USA; [8]University Clinical Hospital Center Bezanijska Kosa, Belgrade, Serbia; [9]Guangdong Lung Cancer Institute, Guangzhou, China; [10]Ipsen, Cambridge, MA, USA; [11]Hospital Universitario 12 de Octubre, H120-CNIO Lung Cancer Unit, Universidad Complutense and Ciberonc, Madrid, Spain; [12]University of Colorado School of Medicine, Aurora, CO, USA

Organisers: ESMO, IASLC

Partners: ESTRO, ETOP·IBCSG PARTNERS

RESILIENT[a] Part 2: Study design, endpoints and statistics

N = 461

Key inclusion criteria

- Histologically or cytologically confirmed SCLC
- Radiologically confirmed progression after 1L platinum-based chemotherapy[b]
- ECOG PS 0 or 1

R 1:1

Stratification factors

- Region
- Platinum sensitivity
- ECOG PS 0 or 1
- Prior immunotherapy

Liposomal irinotecan[c]
70 mg/m² IV Q2W (6-week cycle)

Topotecan[c]
1.5 mg/m²/day IV for 5 days Q3W (6-week cycle)

Tumour assessment every 6 weeks per RECIST v1.1 or RANO BM[d]

Treatment until disease progression or unacceptable toxicity[e]

Follow-up every 4 weeks until death, loss to follow-up, withdrawal of consent, or study end[f]

Primary endpoint: OS

Key secondary endpoints: PFS, ORR per BICR

Statistical analysis: Log-rank test (stratified by region and platinum sensitivity) with 1-sided significance level of 0.023; analyzed after 350 OS events with a stepwise hierarchical approach for secondary endpoints

[a]NCT03088813. [b]One line of immunotherapy in the first- or second-line setting was allowed. [c]Crossover between treatment arms was not permitted. [d]Until radiologically confirmed disease progression. [e]Patients were allowed to take treatment holidays and resume study treatment under certain circumstances. [f]The study was completed once all patients had discontinued treatment and at least 350 OS events had occurred.
1L, first line; BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q2W, every 2 weeks; Q3W, every 3 weeks; R, randomized; RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases; RECIST, Response Evaluation Criteria in Solid Tumors; SCLC, small cell lung cancer.

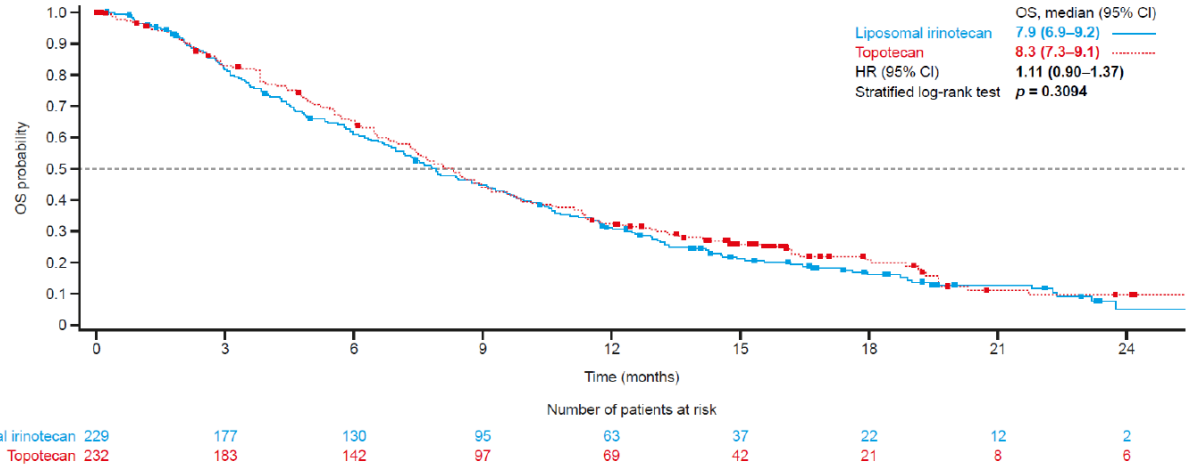
RESILIENT Part 2: ORR per BICR (ITT population)

	Liposomal irinotecan (n = 229)	Topotecan (n = 232)
ORR, % (95% CI)	**44.1 (37.6–50.8)**	**21.6 (16.4–27.4)**
Difference in ORR, % (95% CI); *p* value	**22.3 (14.0–30.6); nominal *p* < 0.0001**	
Best overall response, %		
Complete response	5.2	3.0
Partial response	38.9	18.5
Stable disease	29.7	42.2
Progressive disease	12.2	21.6
Not evaluable	12.7	13.8
Undefined	1.3	0.9
Median DOR, months (95% CI)	4.1 (3.1–4.3)	4.2 (2.9–4.8)

- The 95% CIs for ORR in the liposomal irinotecan and topotecan arms did not overlap

BICR, blinded independent central review; CI, confidence interval; DOR, duration of response; TT, intent-to-treat; ORR, objective response rate.

RESILIENT Part 2: OS (ITT population)



Median follow-up was 18.4 months. Stratified by region (North America/Asia/other), platinum sensitivity (sensitive/resistant), ECOG PS (0/1), prior immunotherapy (yes/no) per IRT, with 1-sided significance level of 0.023.
CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; IRT, interactive response technology; ITT, intention-to-treat; OS, overall survival.

Phase Ib/II Seneparib (PARPinh)+ temozolamida in relapsed SCLC

Study design

Part 1

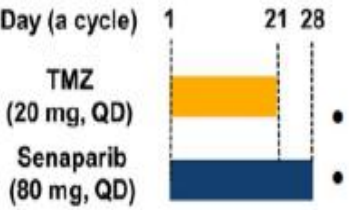
RP2D

Part 2

Simon 2-stage design

Stage 1 N=40

Stage 2: If ≥ 9 responders in Stage 1, expand to N=100



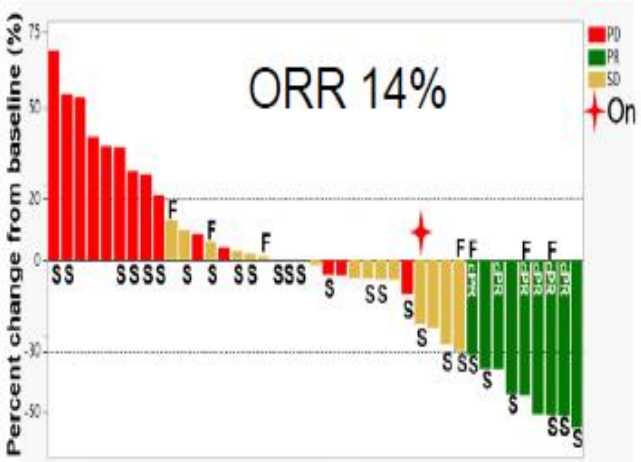
Key eligibility

- ES-SCLC, disease progression after only one prior 1L standard platinum-based therapy
- ECOG 0-2
- At least 1 measurable lesions
- Untreated/unstable brain metastasis will be excluded

Primary endpoint: ORR per RECIST v1.1

Efficacy

Best change from baseline in Target lesions



S: platinum-sensitive; F: FANC mut; one patient was not shown as the target lesions were not evaluable post-baseline.

	FANC WT (n=38)	FANC mut (n=7)
Confirmed ORR	8.6% (3/35)	42.9% (3/7)
mDOR (months) (95% CI)	4.0 (3.4, NR)	5.6 (3.9, NR)

- FANC WT: no pathogenic mutation in FANC genes;
- FANC mut: at least one pathogenic mutation in FANC genes, including FANCA, FANCD1(BRCA2), FANCL, FANCM, et al.

Median follow-up: 8.3 months (0.6-18.7)

Median time to response: 1.8 months (1.7-2.0)

Median duration of response: 4.8 months (95% CI, 3.9- NR)

Min hee Hong,et al. IASLC 2023

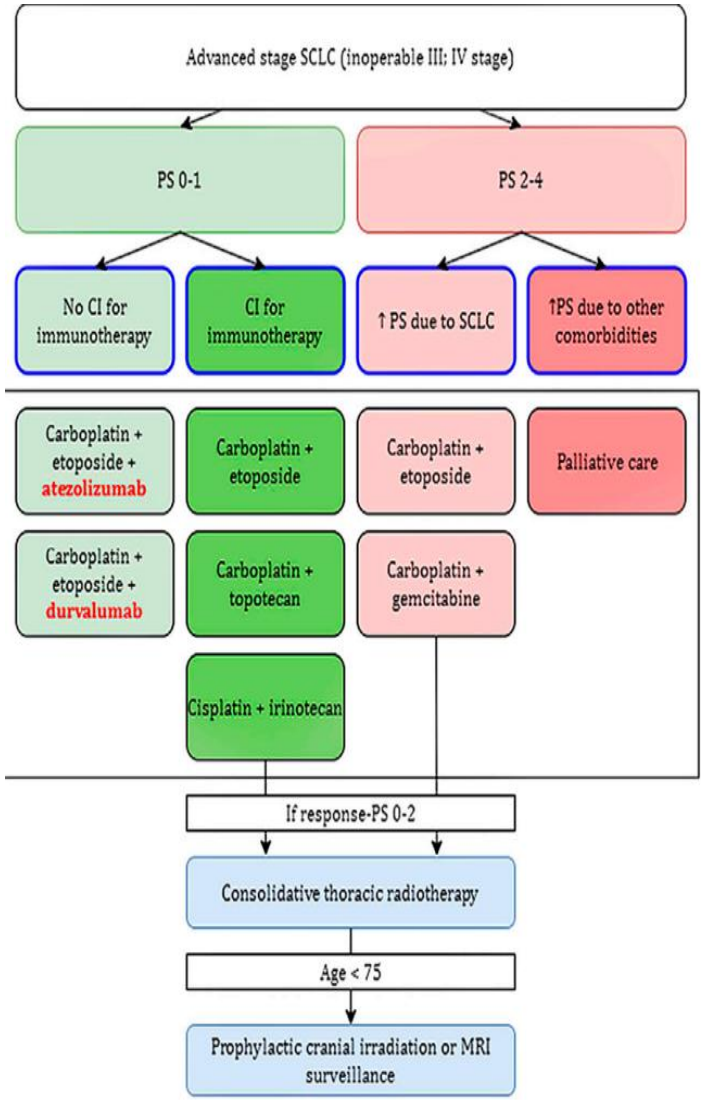
Adelantos y novedades presentes y futuras en SCLCC

.- Inmunoterapia

.- Target

.- Target + IO

.- ADCs



Skopelidou V,. Potential predictors of immunotherapy in small cell lung cancer. Pathol Oncol Res. 2023 May 3;29:1611086.

ETER701. Benmelstobart + anlotinib + CT 1 line ES-SCLC

Key Eligibility Criteria

- 18-75 years
- Pathologically confirmed diagnosis of ES-SCLC
- No prior systemic therapy
- Measurable lesion (RECIST1.1)
- Asymptomatic or treated and stable brain metastases permitted
- ECOG PS 0 or 1
- Adequate organ function

R (1:1:1)
N=738

Induction (Four 21-day cycles)	Maintenance*
Benmelstobart (1200mg, d1) + Anlotinib (12mg, d1-14) + Etoposide + Carboplatin	Benmelstobart + Anlotinib
Placebo + Anlotinib (12mg, d1-14) + Etoposide + Carboplatin	Placebo + Anlotinib
Placebo + Placebo + Etoposide + Carboplatin	Placebo +Placebo

Primary Endpoints
- OS (IRC, RECIST1.1)
- PFS (IRC, RECIST1.1)

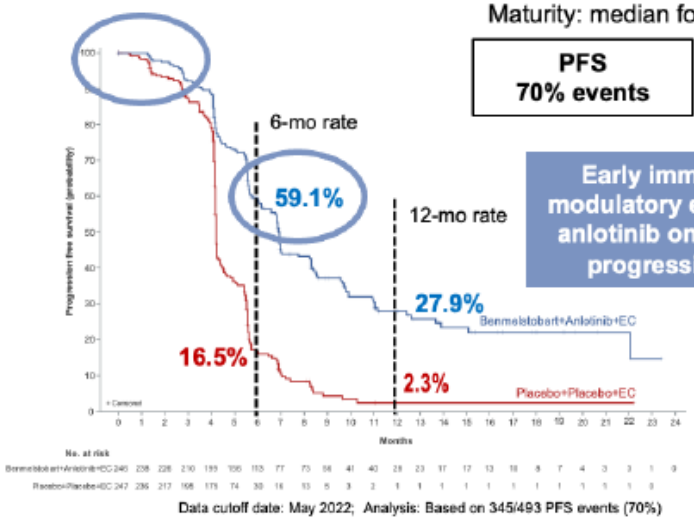
Secondary Endpoints
- PFS (investigator, RECIST1.1 and iRECIST)
- ORR
- DCR
- DOR
- 6-mo/12-mo PFS rate
- 12-mo/18-mo OS rate
- Quality of Life
- Safety and tolerability

➢ **Stratified by:** ECOG PS (0/1); brain metastases (Y/N); liver metastases (Y/N).

	Events n (%)	Median PFS, mo (95%CI)	Hazard ratio (95% CI)	*P*-value
Benmelstobart+Anlotinib+EC	146 (59.35)	6.9 (6.18-8.25)	0.32 (0.26-0.41)	0.0001 *
Placebo+Placebo+EC	199 (80.57)	4.2 (4.17-4.24)		

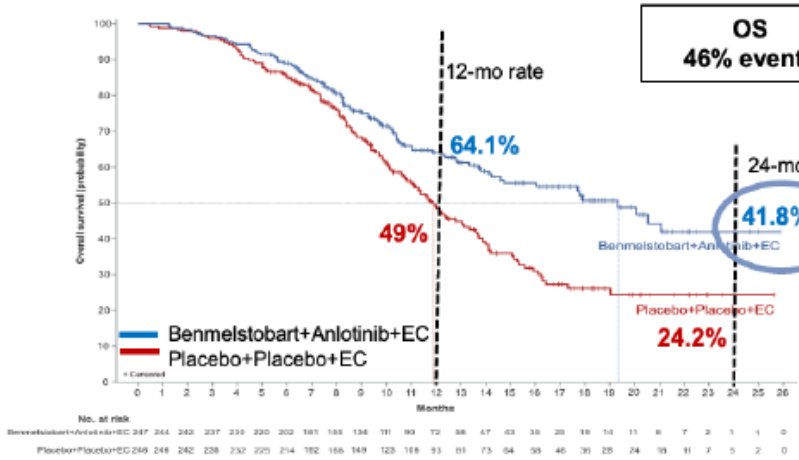
	Events n (%)	Median OS, mo (95%CI)	Hazard ratio (95% CI)	*P*-value
Benmelstobart+Anlotinib+EC	95 (38.62)	19.32 (14.23-NE)	0.61 (0.46-0.79)†	0.0002*
Placebo+Placebo+EC	134 (54.25)	11.89 (10.74-13.37)		

Maturity: median follow-up 14.0 months (range, 12.8-15.5)



Early immune-modulatory effect of anlotinib on tumor progression?

Data cutoff date: May 2022; Analysis: Based on 345/493 PFS events (70%)



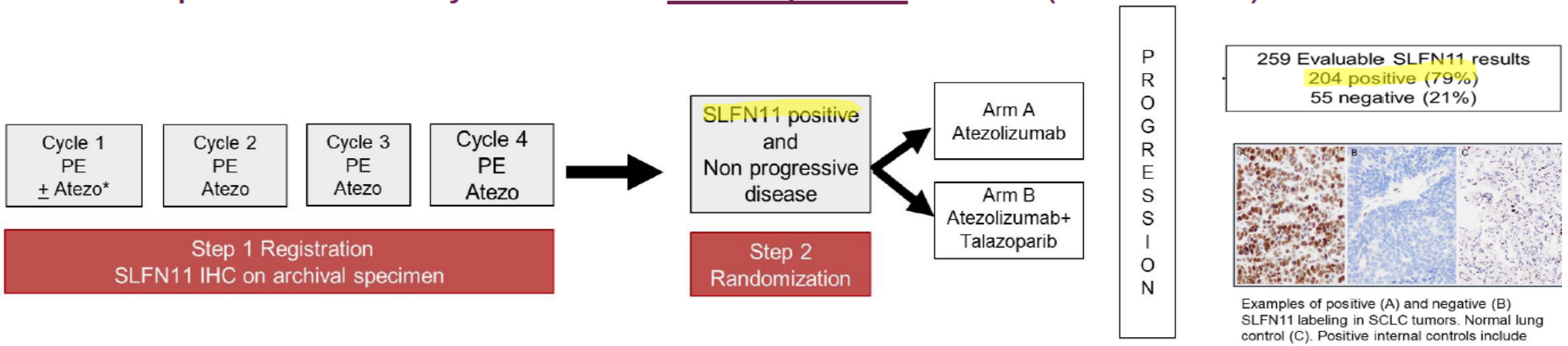
Immature OS

Data cutoff date: May 2022; Analysis: Based on 229/493 OS events (46%)

STUDY LIMITED TO ASIAN PATIENTS

1.- Cheng Y, et al. WCLC 2023

S1929: A Phase 2 Study of Maintenance ATEZOLIZUMAB vs ATEZOLIZUMAB plus TALAZOPARIB in patients molecularly selected with SLFN11 positive ES-SCLC (NCT04334941)



259 Evaluable SLFN11 results
204 positive (79%)
55 negative (21%)

Examples of positive (A) and negative (B) SLFN11 labeling in SCLC tumors. Normal lung control (C). Positive internal controls include endothelial cells (as in B) and lung macrophages (as in C).

Hypothesis: The addition of talazoparib to maintenance atezolizumab will improve PFS in SLFN11+ SCLC.

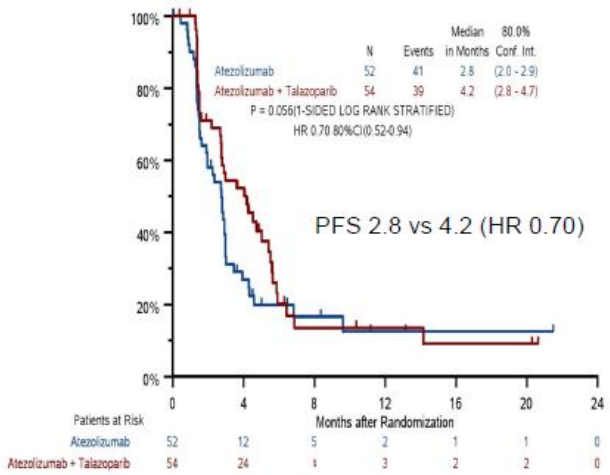
Primary Endpoint: PFS
Secondary endpoints: OS, ORR, AE.
TM Objective: To bank specimens for future correlative studies.

Best Response in Evaluable Patients

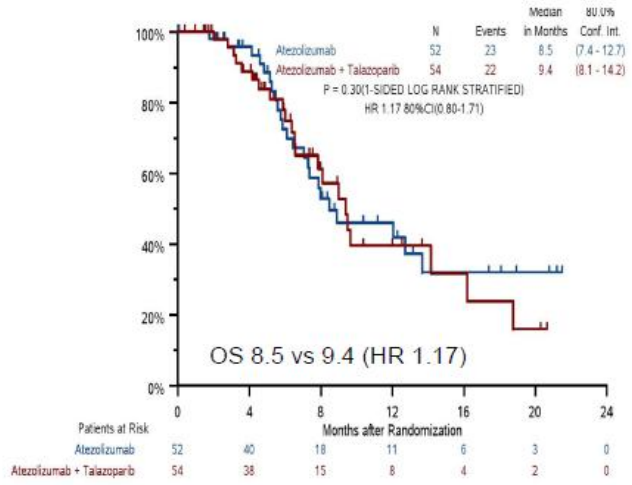
Best Response	Atezolizumab (N=32)	Atezolizumab Talazoparib (N= 34)	Total (N=66)	P-value (one sided)
Partial Response (confirmed + unconfirmed)	5 (16%)	4 (12%)	9 (14%)	
Stable	17 (53%)	16 (47%)	33 (50%)	
Progressive Disease	10 (31%)	12 (35%)	22 (33%)	
Assessment Inadequate	0	2 (6%)	2 (3%)	
Response Rate (80% CI)	16% (8-27)	12% (5-22)	14% (8-21)	0.32
Disease Control Rate (80% CI)	69% (55-80)	59% (46-70)	64% (55-72)	0.27

7 patients have pending assessments
33 patients had CR or non measurable disease at the time of enrollment into the study
All these were excluded from response rate analysis.

Progression-Free Survival



Preliminary OS

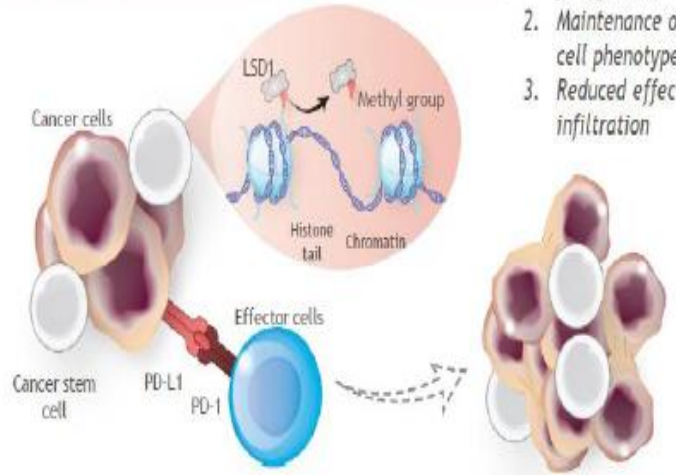


Higher hematologic toxicity with the combination of A+ T (4% vs 15%)

Karim NA, et al. ASCO 2023

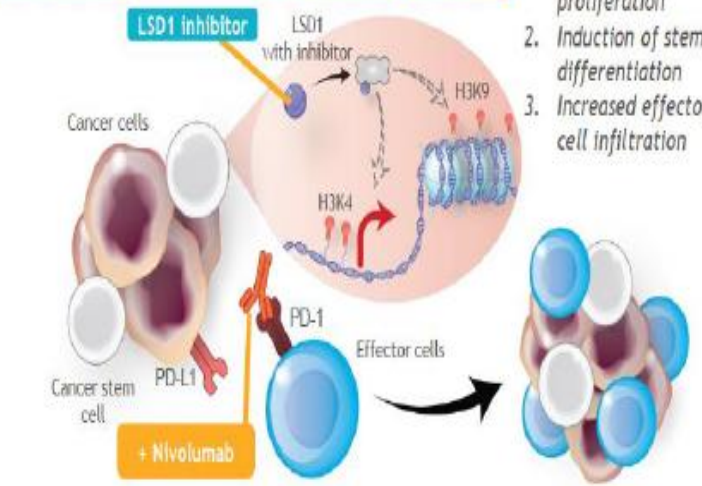
Phase II CC-90011, an LSD1 inh + nivolumab in SCLC

LSD1 biology



1. *Increased tumor cell proliferation*
2. *Maintenance of stem cell phenotype*
3. *Reduced effector cell infiltration*

Therapeutic intervention under investigation



1. *Decreased tumor cell proliferation*
2. *Induction of stem cell differentiation*
3. *Increased effector cell infiltration*

Key eligibility criteria:

- ≥ 18 years old
- ES SCLC or stage IIIb or IV sqNSCLC
- One or 2 prior lines
- For cohorts B and C: must have progressed during ICI therapy
- ECOG PS 0 or 1
- Pre-dose tumor biopsy and on-treatment at C1D22 required

Primary endpoint:

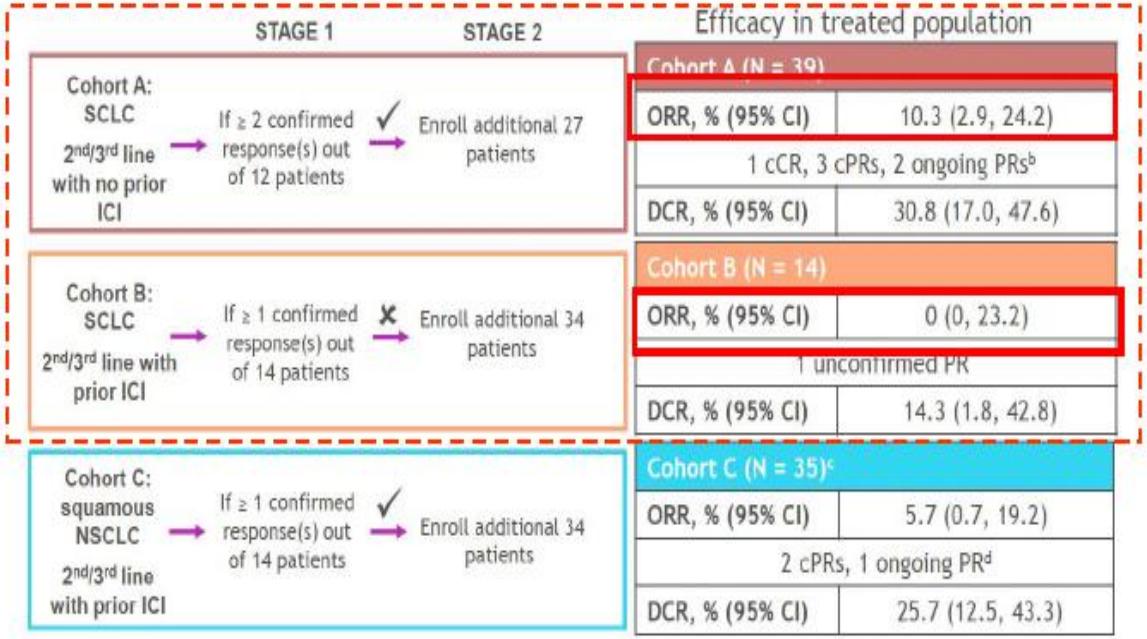
- ORR, per RECIST v1.1

Key secondary endpoints:

- Safety/tolerability
- DOR

Study intervention (28-day cycles):

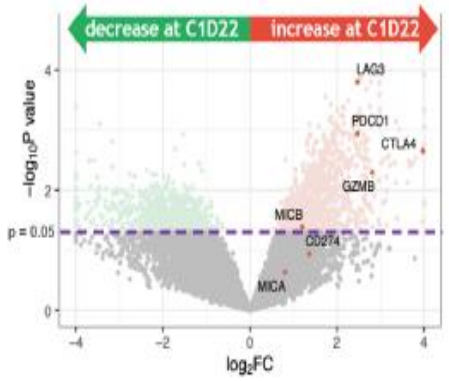
- NIVO 480 mg Q4W IV
- CC-90011 40 mg[a] QW PO



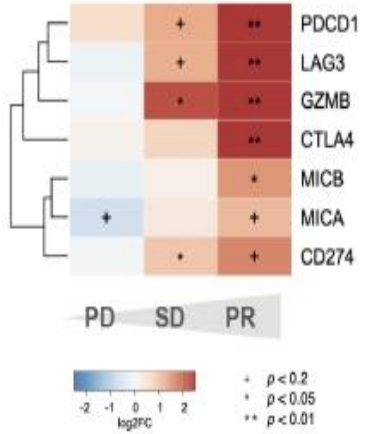
Efficacy in treated population

Cohort A (N = 39)	
ORR, % (95% CI)	10.3 (2.9, 24.2)
1 cCR, 3 cPRs, 2 ongoing PRs[b]	
DCR, % (95% CI)	30.8 (17.0, 47.6)
Cohort B (N = 14)	
ORR, % (95% CI)	0 (0, 23.2)
1 unconfirmed PR	
DCR, % (95% CI)	14.3 (1.8, 42.8)
Cohort C (N = 35)[c]	
ORR, % (95% CI)	5.7 (0.7, 19.2)
2 cPRs, 1 ongoing PR[d]	
DCR, % (95% CI)	25.7 (12.5, 43.3)

Immune-related genes activated post treatment in responders

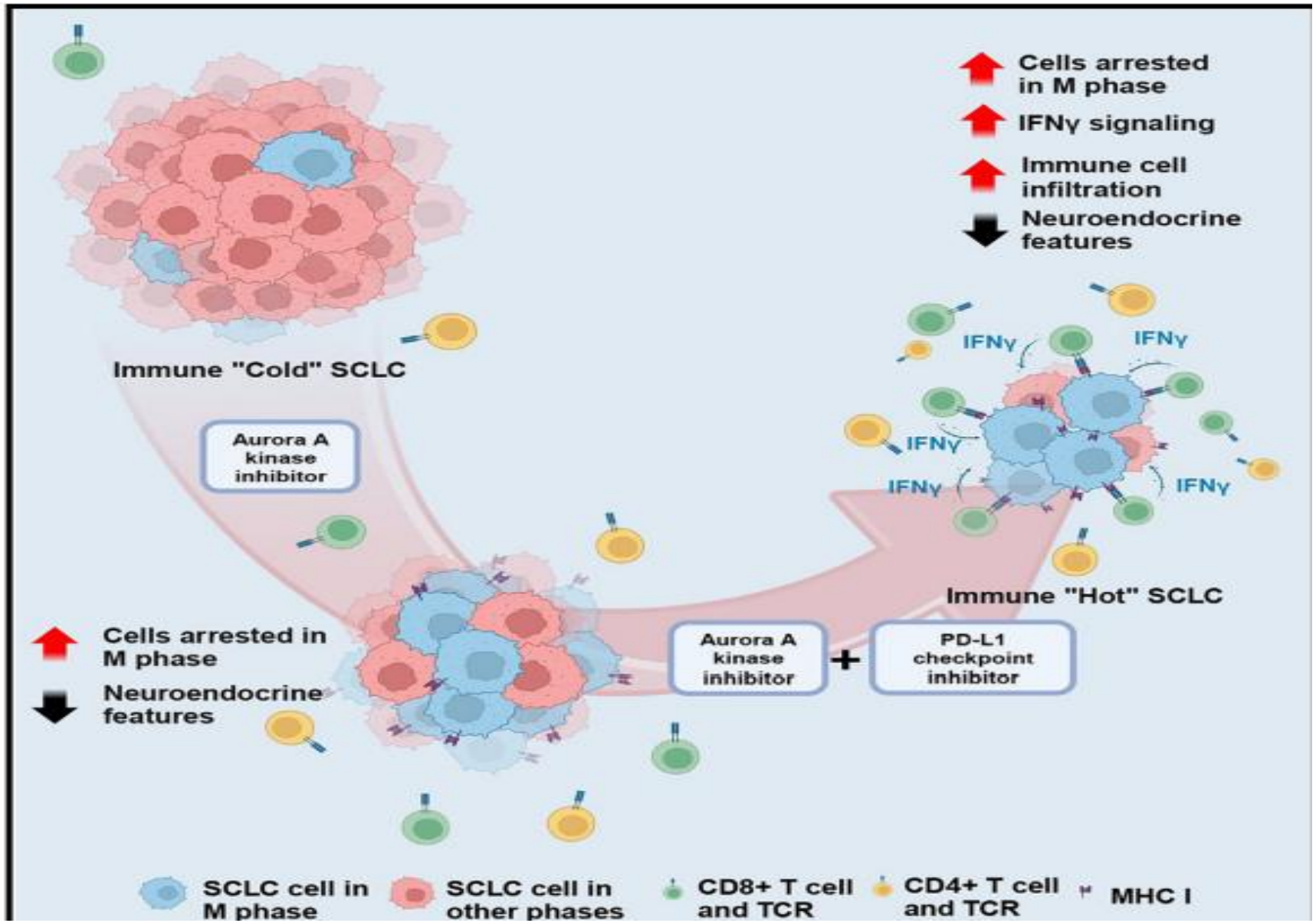


Immune activation in on-treatment biopsies



Rudim CM, et al. IASLC 2023

Aurora A kinase inhibition + PD-L1 immunotherapy



Aurora A kinase inhibition causes accumulation of SCLC tumor cells in mitosis with high expression of antigen-presentation genes mimicking an immunotherapyresponsive inflamed tumor cell state. This promotes T-lymphocyte infiltration, and Aurora A kinase inhibition + PD-L1 has durable efficacy in immunocompetent SCLC mouse models.

Aurora A kinase inhibition + PD-L1 immunotherapy has durable efficacy in SCLC models.
increases T-lymphocyte infiltration in tumors
Blocks tumor cells in mitosis with high interferon signaling and MHC class I

Li Y, eta al Aurora A kinase inhibition induces accumulation of SCLC tumor cells in mitosis with restored interferon signaling to increase response to PD-L1. Cell Rep Med. 2023 Nov 21;4(11):101282. doi: 10.1016/j.xcrm.2023.101282.

Lurbinectidine + Pembrolizumab in Relapsed SCLC. Phase I/II LUPER trial

- 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] Garcia-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)

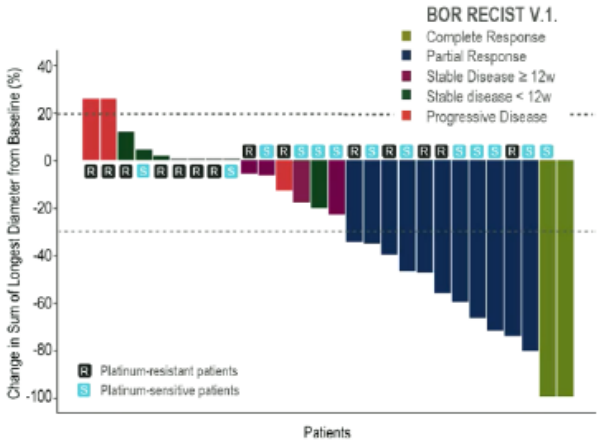
Antonio Calles, et al. ESMO 23

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)

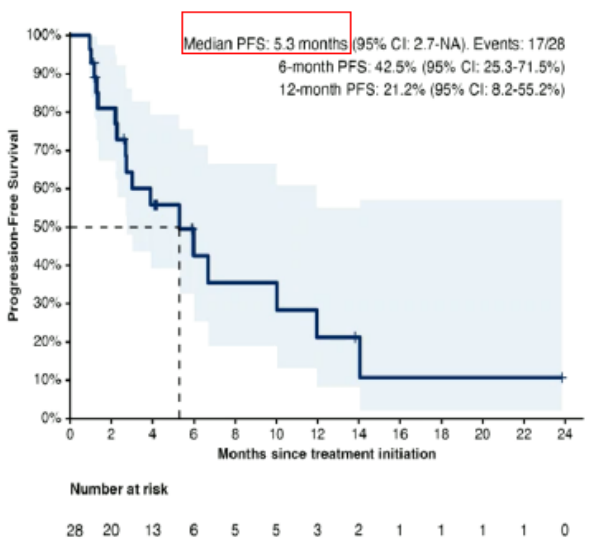
Tumor response, n (%)	Platinum-free interval <90 days (n = 14)	Platinum-free interval ≥90 days (n = 13)	Overall (N = 28)
Best Overall Response			
CR*	0 (0%)	1 (7.7%)	2 (7.1%)
PR	5 (35.7%)	6 (46.2%)	11 (39.3%)
SD ≥ 12w	1 (7.1%)	3 (23.1%)	4 (14.3%)
SD < 12w	2 (14.3%)	2 (15.4%)	4 (14.3%)
PD	3 (21.4%)	0 (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%)

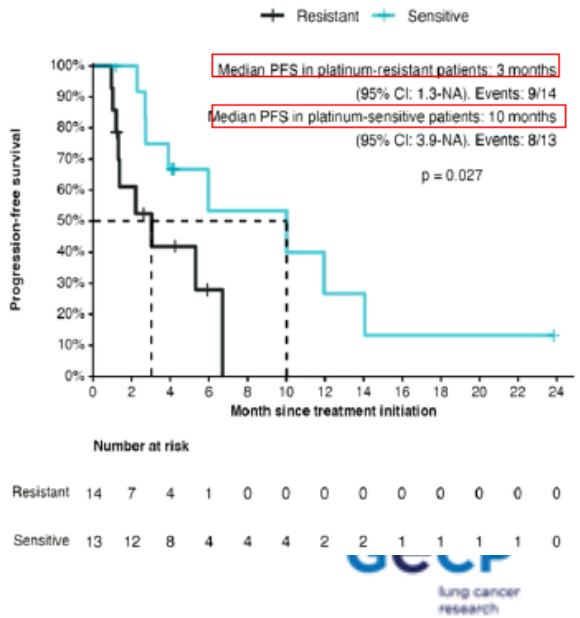


n (%), number of patients (percentage based on N); N, number of patients in the population; CR, Complete response; PR, Partial response; SD, Stable disease; PD, Progressive disease; NE, Not evaluated; *Information on the platinum-free interval of

Results

Progression-Free Survival (PFS)





Calles A. ESMO 2023

Lurbinectidine + Pembrolizumab in Relapsed SCLC. Phase I/II LUPER trial

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

Organizado por: GECP lung cancer research

Calles A. ESMO 2023

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

Courtesy Manuel Dómine

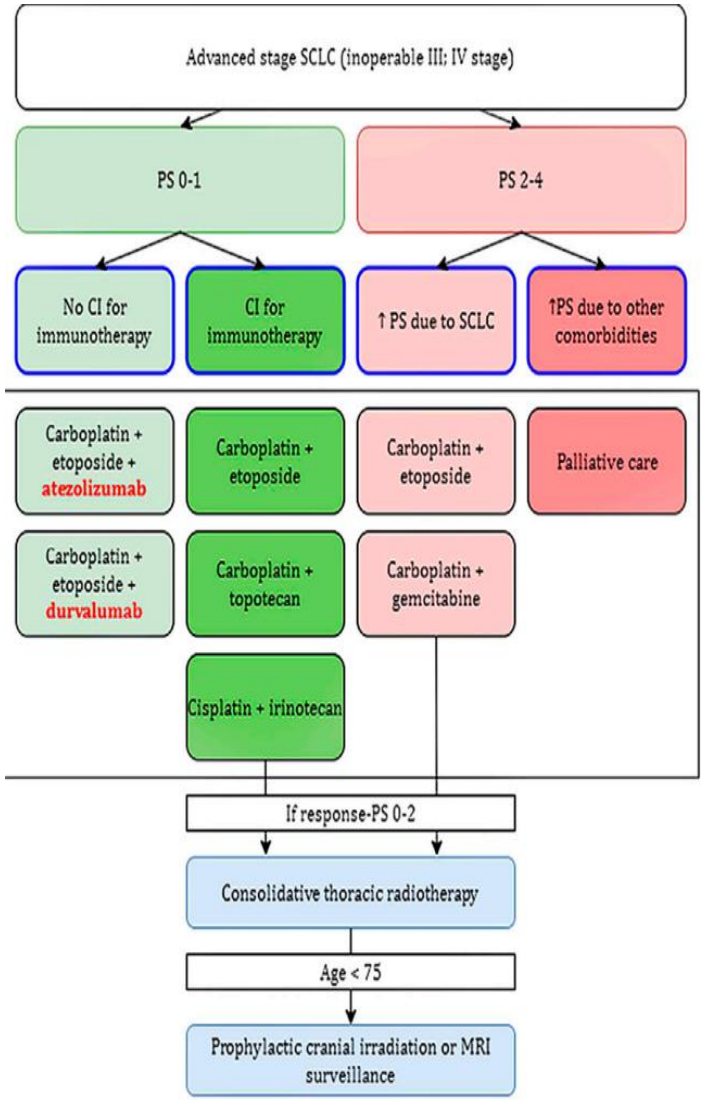
Adelantos y novedades presentes y futuras en SCLCC

.- Inmunoterapia

.- Target

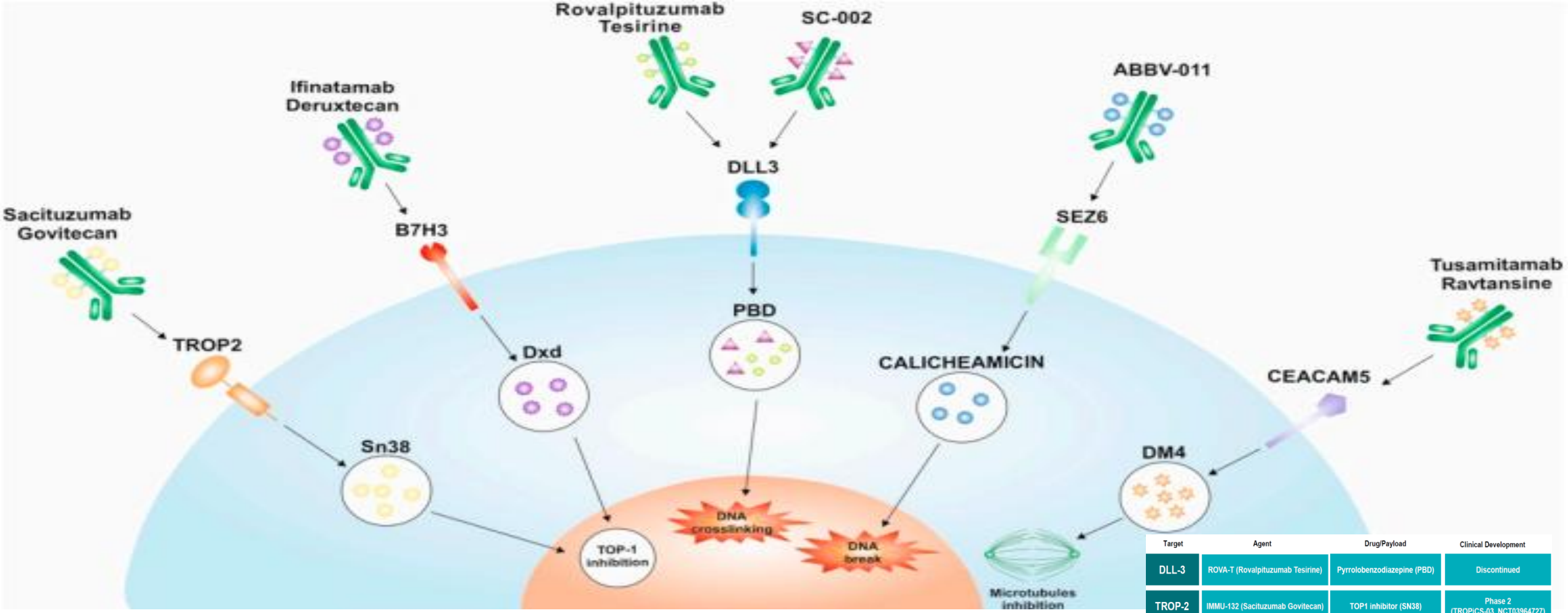
.- Target + IO

.- ADCs



Skopelidou V,. Potential predictors of immunotherapy in small cell lung cancer. Pathol Oncol Res. 2023 May 3;29:1611086.

ADCs en Ca microcítico pulmón. Una nueva visión



Target	Agent	Drug/Payload	Clinical Development
DLL-3	ROVA-T (Rovalpituzumab Tesirine)	Pyrrolobenzodiazepine (PBD)	Discontinued
TROP-2	IMMU-132 (Sacituzumab Govitecan)	TOP1 inhibitor (SN38)	Phase 2 (TROPiCS-03, NCT03964727)
SEZ6	ABBV-011 ABBV-706	Calicheamicin (DNA-damaging) TOP1 inhibitor	FIH/Phase 1 (NCT03639194) FIH/Phase 1 (NCT05599984)
B7-H3	DS-7300 (Ifinatamab deruxtecan) ABBV-155 (Mirzotamab clezutoclax)	TOP1 inhibitor (DXd) BCL2/XL inhibitor (Clezutoclax)	FIH/Phase 1-2 (NCT05280470) Phase 1 (NCT03595059)
CEACAM5	SAR408701 (Tusamitamab Ravtansine)	MT inhibitor (Maytansinoid DM4)	Phase 1 (NCT02187848)

Belluomini L, Sposito M, Avancini A, Insolda J, Milella M, Rossi A, Pilotto S. Unlocking New Horizons in Small-Cell Lung Cancer Treatment: The Onset of Antibody-Drug Conjugates. Cancers (Basel). 2023 Nov 10;15(22):5368. doi: 10.3390/cancers15225368.

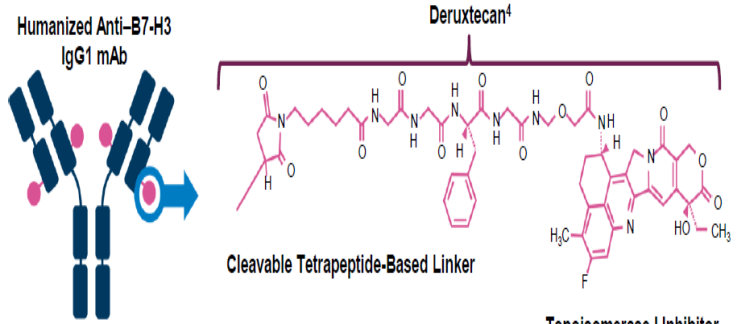
Ifnatalamab deruxtecan in SCLC

Novel treatment approaches

Ifinatamab Deruxtecan (I-DXd/DS-7300) in SCLC

Ifinatamab deruxtecan (I-DXd) is an ADC with 3 components

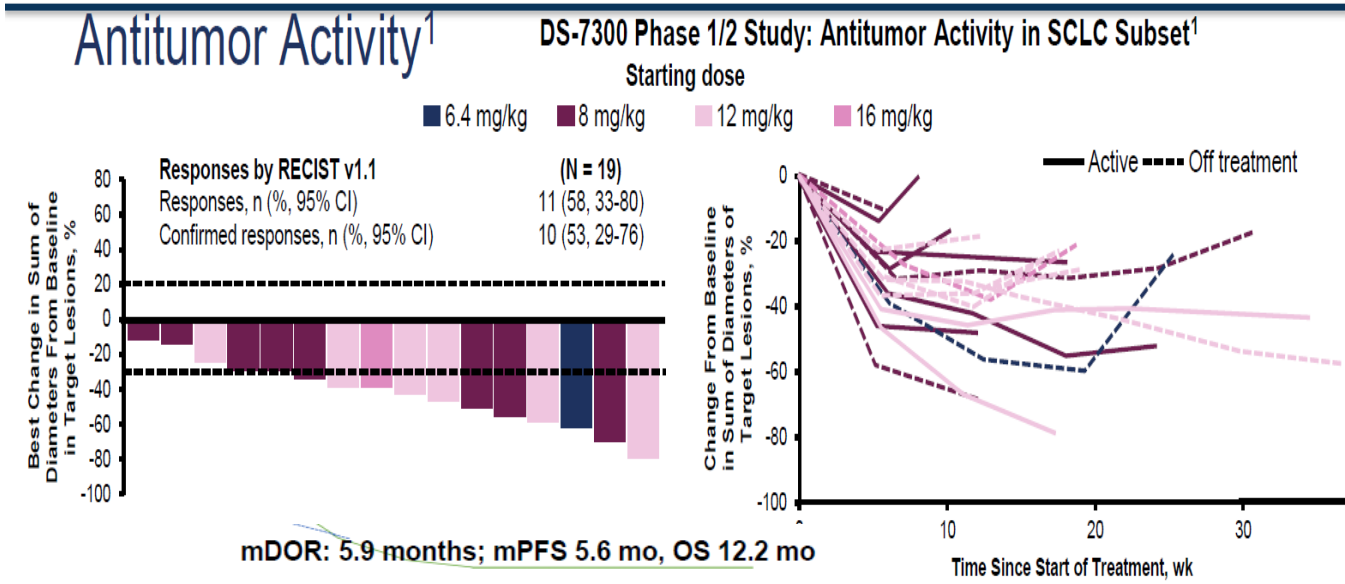
- A fully human anti-B7-H3 IgG1 mAb attached to
- A topoisomerase I inhibitor payload and an exatecan derivative via
- A tetrapeptide-based cleavable linker



Doi T. et al. ESMO Congress 2022

- Payload mechanism of action: topoisomerase I inhibitor
- High potency of payload
- Optimized DAR ~4
- Payload with short systemic half-life
- Stable linker payload
- Tumor-selective cleavable linker
- Bystander antitumor effect

Ifinatalamab Deruxtecan (I-DXd/DS-7300) in SCLC: Antitumor Activity[1]



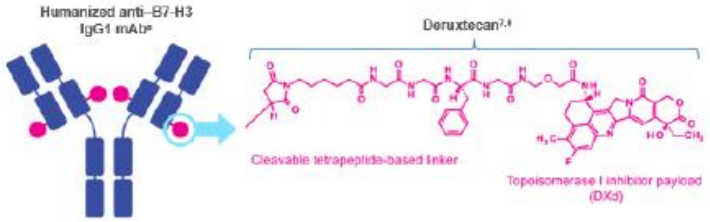
	Part 1 Escalation					Part 2 Expansion	Study Total
	4.8 mg/kg (n = 5)	6.4 mg/kg (n = 8)	8.0 mg/kg (n = 19)	12.0 mg/kg (n = 33)	16.0 mg/kg (n = 16)	12.0 mg/kg (n = 66)	(N = 147)
Treatment duration, median (range), wk	9 (3-15)	14 (3-49)	15 (0-51)	13 (0-59)	14 (0-43)	9 (0-48)	12 (0-59)
Any TEAE, n (%)	5 (100)	8 (100)	19 (100)	32 (97)	16 (100)	64 (97)	144 (98)
TEAE with CTCAE grade ≥3	1 (20)	1 (13)	8 (42)	14 (42)	14 (88)	28 (42)	66 (45)
TEAE associated with drug discontinuation	0	0	4 (21)	2 (6)	2 (13)	3 (5)	11 (8)
TEAE associated with dose interruption	1 (20)	0	0	11 (33)	3 (19)	16 (24)	31 (21)
TEAE associated with dose reduction	0	0	2 (11)	4 (12)	5 (31)	7 (11)	18 (12)
Treatment-related TEAE associated with death	0	0	0	0	1 (6)	0	1 (1)

DS7300-A-J101 Study Design (NCT04145622)

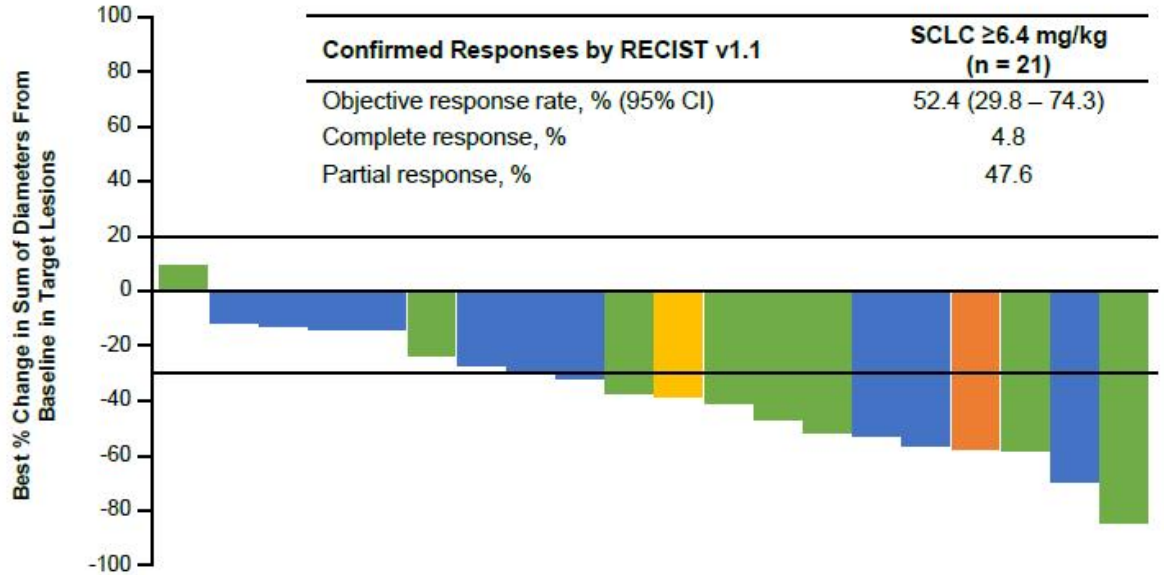
- **We present a subgroup analysis of patients with SCLC (N = 22) from part 1 treated with I-DXd at all doses studied**

Ifinatamab Deruxtecan (I-DXd; DS-7300) Was Designed With 7 Key Attributes

- B7-H3 is overexpressed in a wide range of cancer types and is associated with disease progression and lower survival[1–5]
- I-DXd is a B7-H3 (CD276)-directed ADC composed of 3 parts:[6–9,11]
  - A humanized anti–B7-H3 IgG1 monoclonal antibody[8,11]
  - A topoisomerase I inhibitor payload (an exatecan derivative, DXd)
  - A tetrapeptide-based cleavable linker that covalently bonds the other 2 components



Payload mechanism of action: topoisomerase I inhibitor[7,9,11,b]
High potency of payload[6,11,b]
Optimized drug-to-antibody ratio ≈ 4[6–8,10,b]
Payload with short systemic half-life[8,11,b,c]
Stable linker-payload[8,11,b]
Tumor-selective cleavable linker[8,11,b]
Bystander antitumor effect[7,10,11,b]

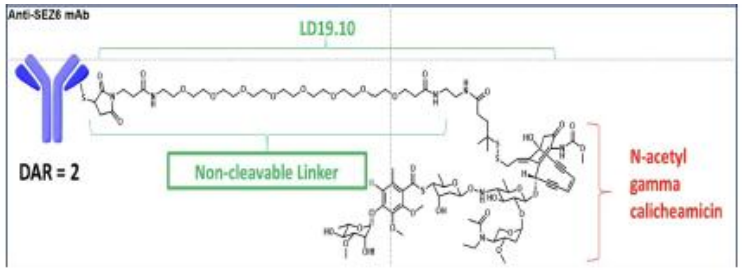


Confirmed Responses by RECIST v1.1	SCLC ≥6.4 mg/kg (n = 21)
Objective response rate, % (95% CI)	52.4 (29.8 – 74.3)
Complete response, %	4.8
Partial response, %	47.6

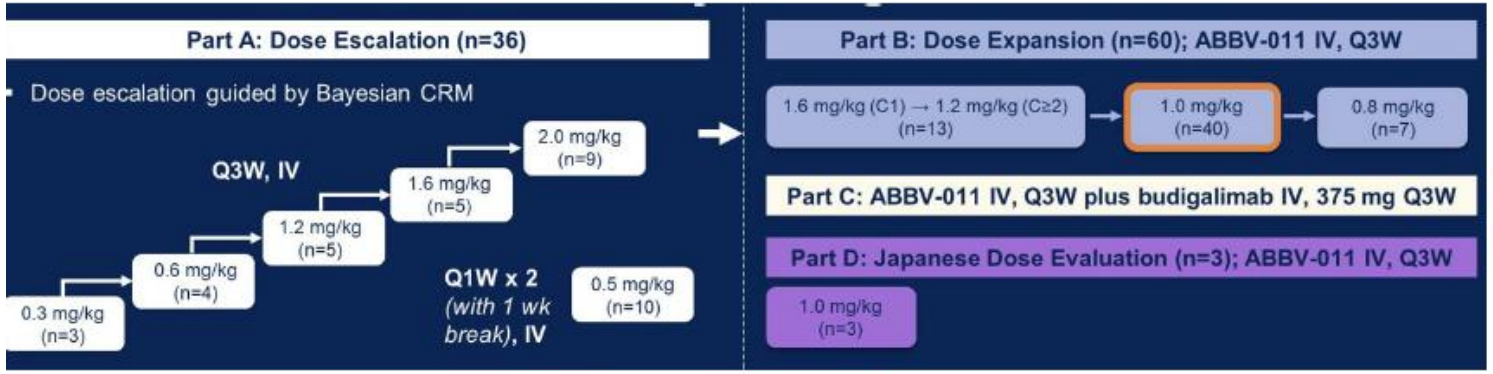
- **52% ORR, 5.9 months mDOR, 5.6 months mPFS, and 12.2 months mOS**
- Nausea was the most common TEAE, and antiemetic prophylaxis is now required for all I-DXd studies, ILD 13.6% (Gr1-2)

Linardou H. IASLC 2023

SEZ6-targeted ADC (ABBV-011) in relapsed SCLC



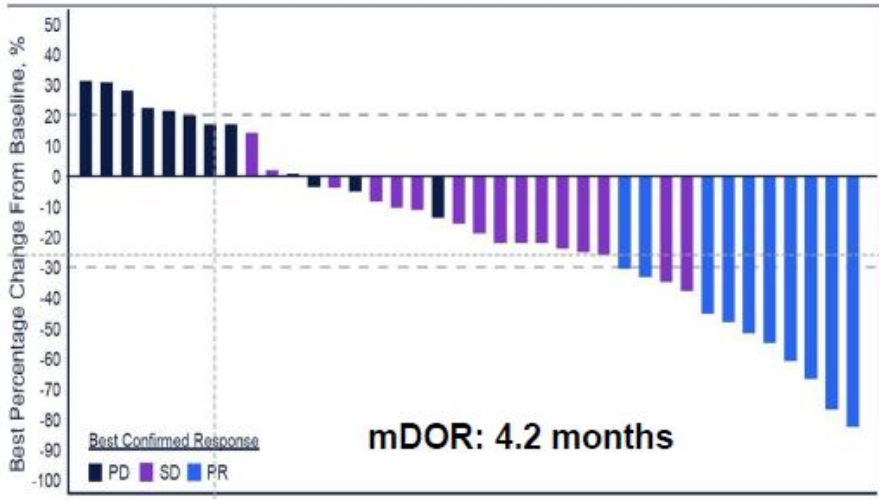
ABBV-011
Calicheamicin payload



	1 mg/kg n=40	Total N=99
Any TEAE, n (%)	39 (98%)	96 (97%)
Grade ≥3 TEAE, n (%)	26 (65%)	63 (64%)
Serious TEAEs, n (%)	18 (45%)	41 (41%)
Treatment-related AEs, n (%)	31 (78%)	76 (77%)
Associated with discontinuation	3 (8%)	13 (13%)
Associated with dose reduction	6 (15%)	8 (8%)
Associated with dose interruption	12 (30%)	29 (29%)

- **TEAE of interest: Hepatotoxicity**
- Delayed onset of hepatotoxicity limited long-term dosing at doses higher than 1.2 mg/kg

Antitumor Activity 1 mg/kg cohort (n=38)



Efficacy Outcome	1 mg/kg n=40
Confirmed ORR, n (%)	10 (25%)
[95% CI]	[13, 41]
CBR, n (%)	26 (65%)
[95% CI]	[48, 79]
CBR lasting >12 weeks, n (%)	17 (43%)
[95% CI]	[27, 59]

GECP lung cancer research

Mongemztem D, et al.ASCO 2023

Sacizutumab- Govitecan in 2ª line ES-SCLC

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)

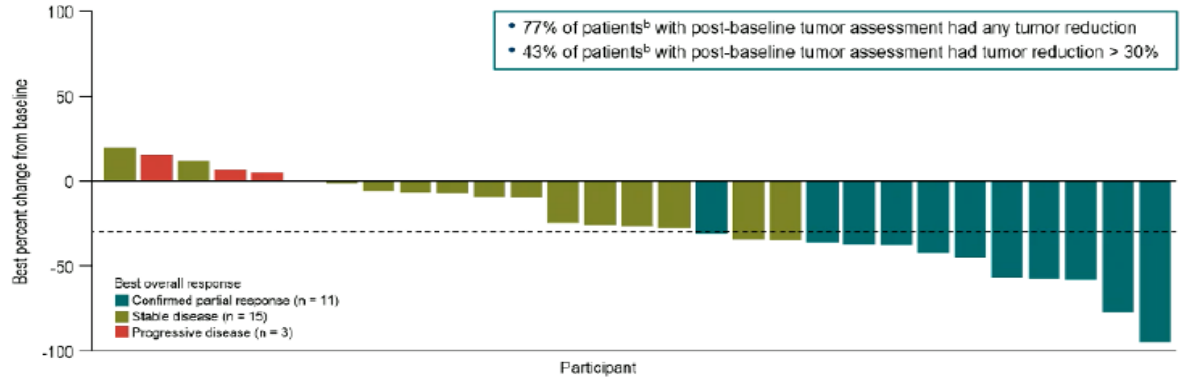
2L, second line; ADC, antibody drug conjugate; BICR, blinded independent central review; CBR, clinical benefit rate; CNS, central nervous system; D, day; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ES-SCLC, extensive stage small cell lung cancer; HER2–, 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]

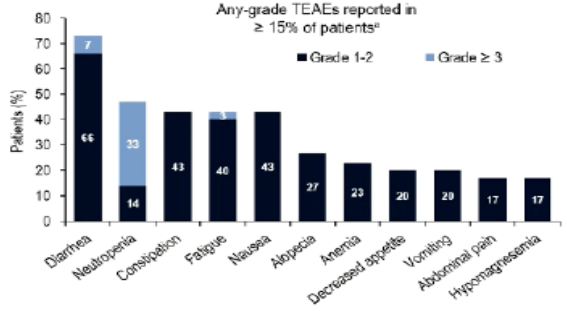


Includes patients enrolled on or before 27 April 2023. RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1. [a]By investigator assessment per RECIST v1.1. [b]Percentages were calculated using the total number of patients (N = 30).

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



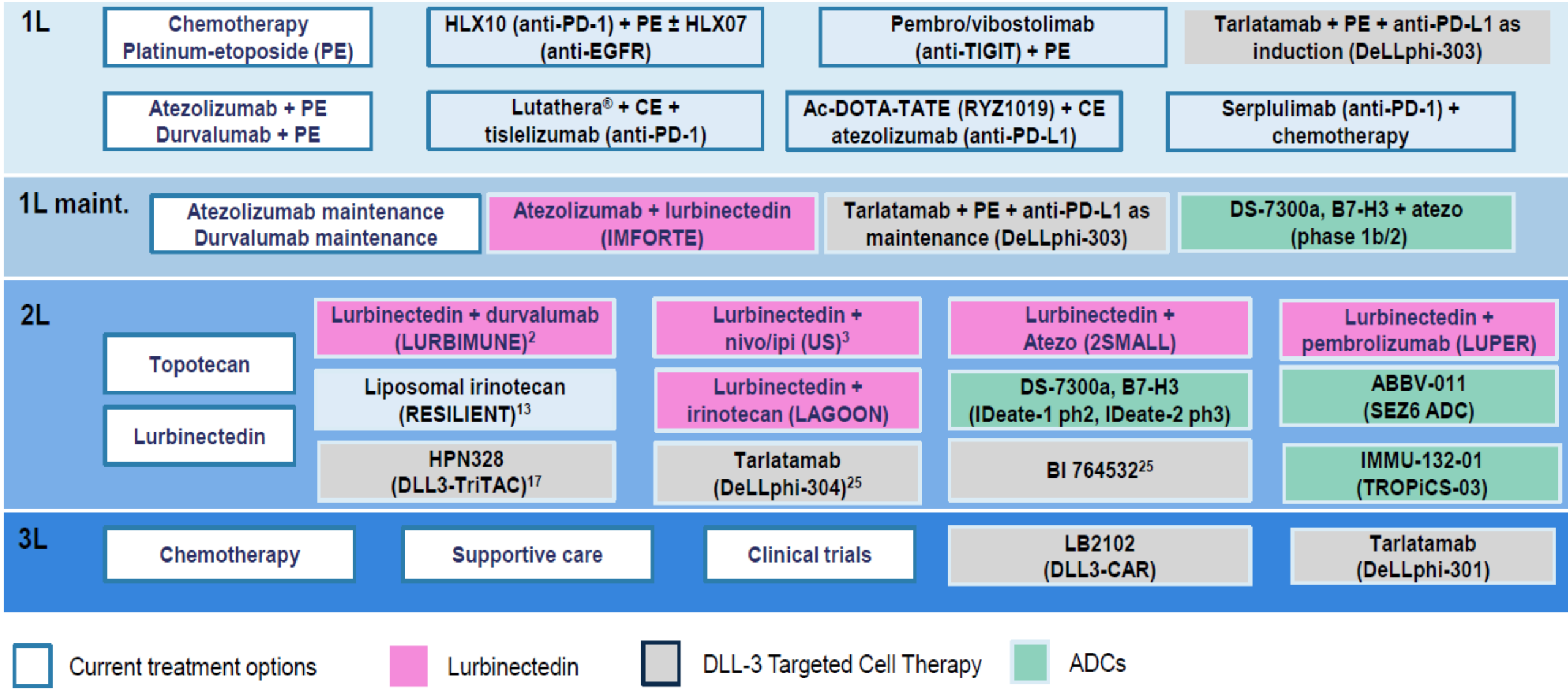
TEAE is defined as any adverse event with an onset date on or after the study treatment start date and no later than 30 days after the last dose of study treatment. ES-SCLC, extensive-stage squamous cell lung cancer; SG, sacituzumab govitecan; TEAE, treatment-emergent adverse event. [a]Includes patients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

lung cancer research

Dowlatin A. ESMO 2023

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

Courtesy Manuel Dómine


1L
Chemotherapy
Platinum-etoposide (PE)
HLX10 (anti-PD-1) + PE ± HLX07 (anti-EGFR)
Pembro/vibostolimab (anti-TIGIT) + PE
Tarlatamab + PE + anti-PD-L1 as induction (DeLLphi-303)
Atezolizumab + PE
Durvalumab + PE
Lutathera® + CE + tislelizumab (anti-PD-1)
Ac-DOTA-TATE (RYZ1019) + CE atezolizumab (anti-PD-L1)
Serplulimab (anti-PD-1) + chemotherapy
1L maint.
Atezolizumab maintenance
Durvalumab maintenance
Atezolizumab + lurbinectedin (IMFORTE)
Tarlatamab + PE + anti-PD-L1 as maintenance (DeLLphi-303)
DS-7300a, B7-H3 + atezo (phase 1b/2)
2L
Topotecan
Lurbinectedin
Lurbinectedin + durvalumab (LURBIMUNE)[2]
Lurbinectedin + nivo/ipi (US)[3]
Lurbinectedin + Atezo (2SMALL)
Lurbinectedin + pembrolizumab (LUPER)
Liposomal irinotecan (RESILIENT)[13]
Lurbinectedin + irinotecan (LAGOON)
DS-7300a, B7-H3 (IDeate-1 ph2, IDeate-2 ph3)
ABBV-011 (SEZ6 ADC)
HPN328 (DLL3-TriTAC)[17]
Tarlatamab (DeLLphi-304)[25]
BI 764532[25]
IMMU-132-01 (TROPiCS-03)
3L
Chemotherapy
Supportive care
Clinical trials
LB2102 (DLL3-CAR)
Tarlatamab (DeLLphi-301)
Current treatment options
Lurbinectedin
DLL-3 Targeted Cell Therapy
ADCs

Mesotelioma

#LBA8505: IND227 phase III (P3) study of cisplatin/pemetrexed (CP) with or without pembrolizumab (pembro) in patients (pts) with malignant pleural mesothelioma (PM): A CCTG, NCIN, and IFCT trial

Phase III, open label

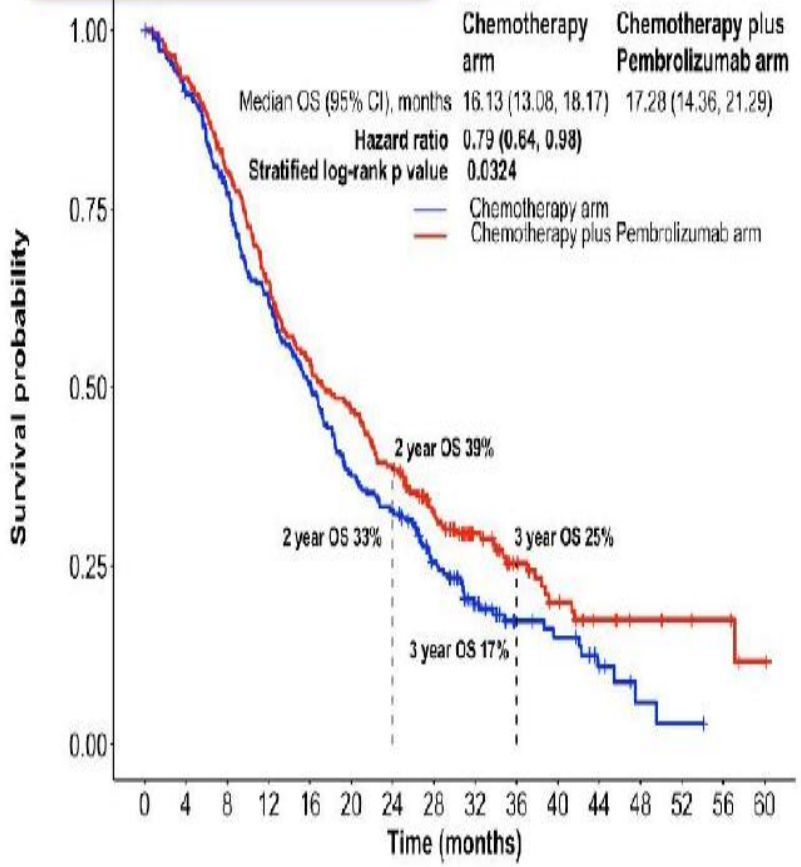
- Chemotherapy naïve pts with PM N=440
  - Stratified by histology Primary endpoint OS
    - Randomize (1 : 1)
      - Platinum-pemetrexed* q3w x 6 cycles
      - Platinum-pemetrexed* q3w x 6 cycles + Pembrolizumab q3w for 2 years

Objectives

PRIMARY:
- Overall Survival

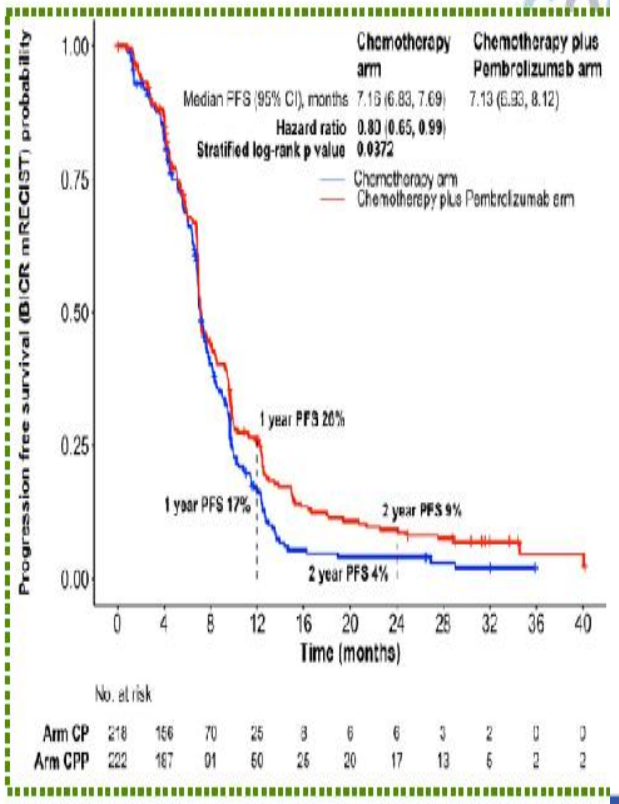
SECONDARY:
- Tolerability
- Response (mRECIST, central review, imagir 6, 12, 18 wks then every 12 wks)
- PFS
- QoL
- Health economics

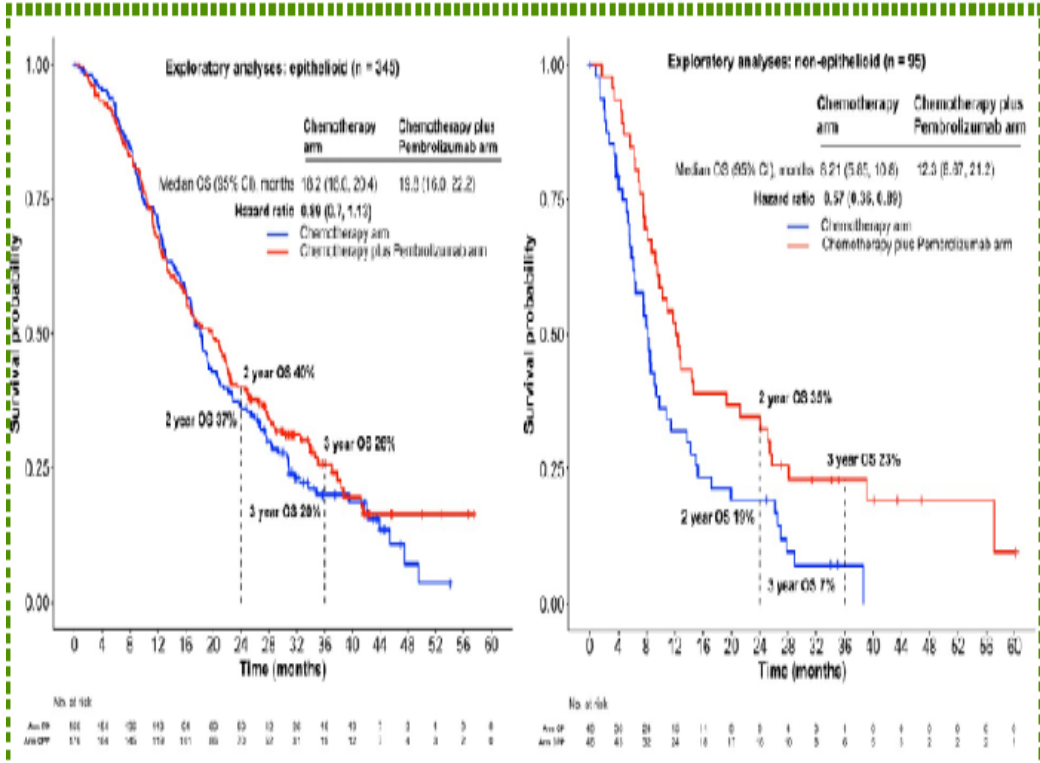
EXPLORATORY:
- Predictive and prognostic value of PD-L1 (Dako 22C3 platform; combined positive score (CPS))
- iRECIST



Best Overall Response (mRECIST, Central Review)

Response		CP (N=218)	CPP (N=222)	P-value
Complete Response		0	2 (1%)	P< 0.0001
Partial Response		83 (38%)	136 (61%)	
Stable disease/non-CR/PD		103 (47%)	70 (32%)	
Disease Progression		11 (5%)	9 (4%)	
Response could not be assigned	Total	21 (10%)	5 (2%)	
	Never treated/WOC[1]	7 (3%)	0	
	Other reasons[2]	9 (4%)	3 (1%)	
	No baseline images uploaded	5 (2%)	2 (1%)	
Duration of CR/PR (mths)	Median (95% CI)	5.5m (4.2-6)	5.8m (5.5-7)	P=0.185
	Range	0.03, 25.1	0.03, 38.9	





Cu, Quincy S. ASCO 2023

Phase 1/2 Randomized Trial of Anetumab Ravtansine and Pembrolizumab Compared to Pembrolizumab for Pleural Mesothelioma

Aaron Mansfield

Study Design

Phase 1 Safety Lead-In
- anetumab ravtansine (6.5 mg/kg iv) and pembrolizumab (200 mg iv) q3weeks

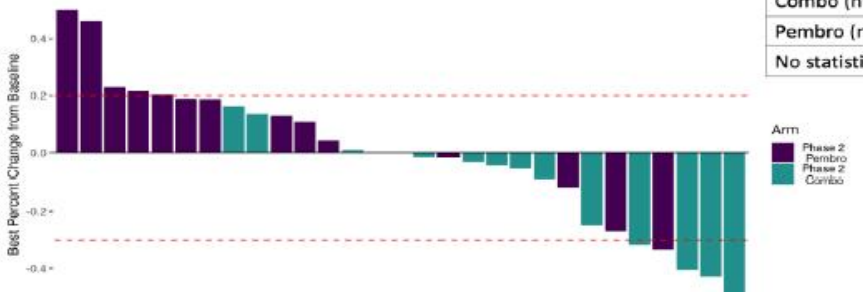
Phase 2 Randomization
- anetumab ravtansine and pembrolizumab
- pembrolizumab

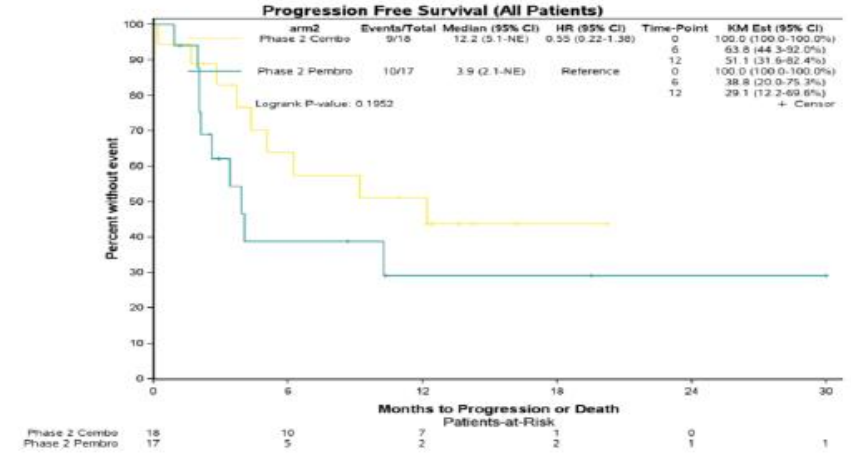
Phase 1
- No prior immunotherapy
- No significant comorbidities or auto-immune conditions
- Epithelioid mesothelioma
- Measurable disease not required

Phase 2
- No prior immunotherapy
- No significant comorbidities or auto-immune conditions
- ≥30% mesothelin expression by tumor cells
- Measurable disease

Phase 2 – Best change from baseline

Arm	PR	SD
Combo (n=18)	2	9
Pembro (n=17)	1	5
No statistical difference in ORR		

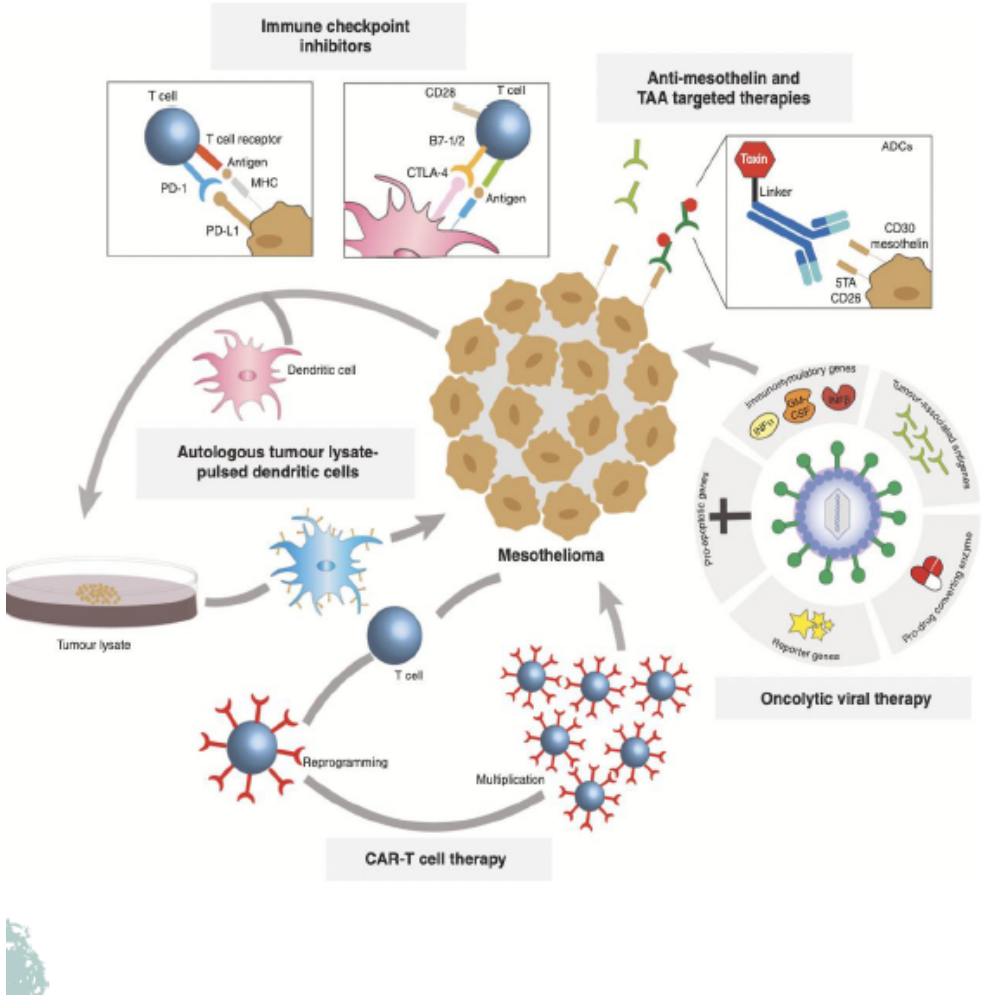




Group 1: Anetumab ravtansine and Pembrolizumab
Group 2: Pembrolizumab

Hazard ratio: 0.55
P value = 0.1952

Target: Mesotelina

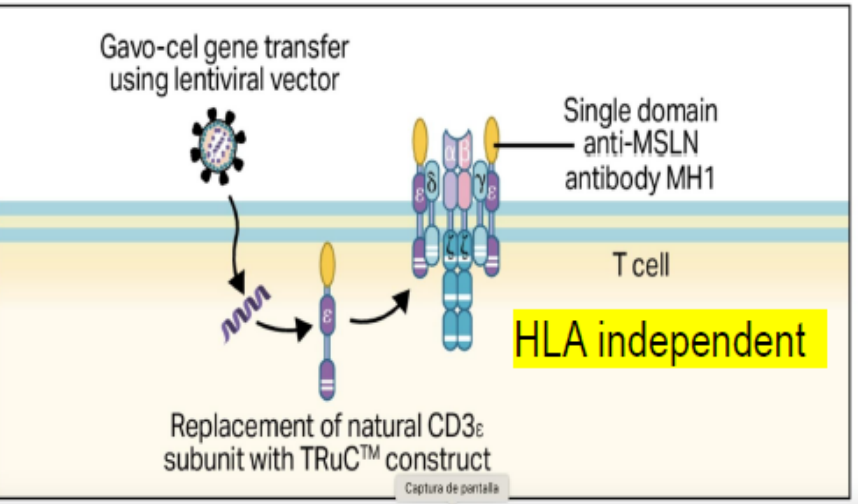


DENTRITIC CELL THERAPY	Study	Clinical Trials ID
DENIM (Allogenic Tumor Cell Lysate, PheraLys)	II-III	NCT03610360
MESODEC (Autologous WT1-targeted Dendritic Cell Vaccine)	I-II	NCT02649829
MESOVAX (Autologous Dendritic Cell Vaccine + Pembro)	I	NCT03546426
VACCINES		
Galinpepimut-S (WT1) + Nivolumab	I	NCT04040231
UV1 (hTERT) + Nivolumab and Ipilimumab (NIPU)	II	NCT04300244
MSLN-TARGETED T-CELL ENGINEERED THERAPY		
MSLN-targeted CAR T-Cells	FIH	NCT04577326 NCT03054298
αPD1-MSLN-CAR T-Cells	I	NCT04489862
Gavo-cel (TC-210) (T-Cell Receptor Fusion Construct TRuC™)	FIH	NCT03907852
HPN536 (T cell-engaging, MSLN/CD3-specific TriTAC)	I/II	NCT03872206
MSLN-DIRECTED ADCs		
BMS-986148	I/II	NCT02341625

Courtesy Dra.Noemi Regart

New Engineered T cells: Phase 1 gavo-cel (TC-210) in refractory MPM and other mesothelin-expressing solid tumors

GAVO-CEL (TC-210) anti-mesothelin (MSLN) T-Cell Receptor Fusion Construct (TRuC™)

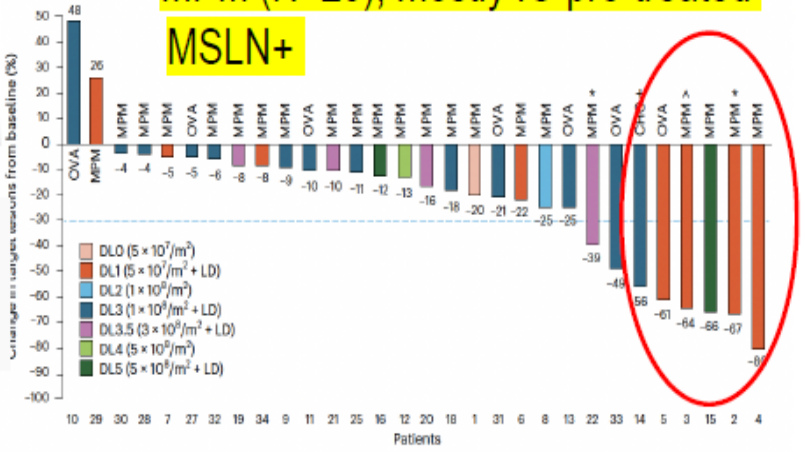


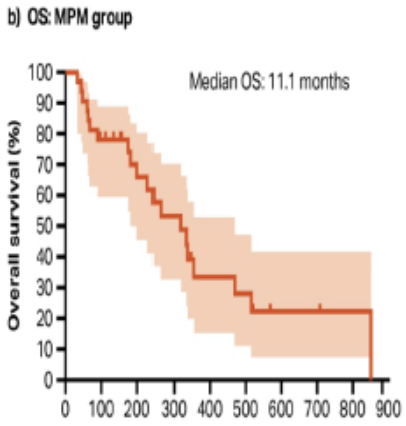
Phase 2 trial ongoing in combination with ICIs in patients with MSLN-expressing solid tumors ongoing (NCT03907852)

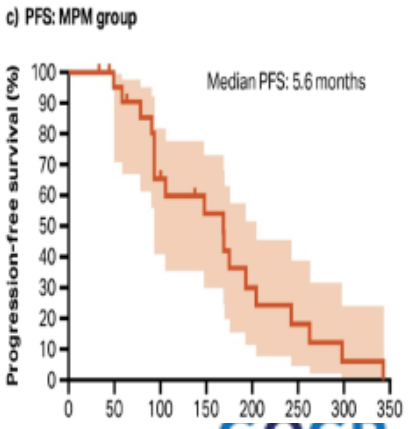
GAVO-CEL (TC-210) Phase 1 Safety and preliminary activity

RP2D Grade ≥TEAEs of interest:
lymphopenia, neutropenia, CRS (25%), pneumonitis (16%), bronchioalveolar hemorrhage
peritoneal/pleural effusions

MPM (N=23), mostly IO pre-treated
MSLN+







Raffit Hassan, et al. Nature Medicine 2023; ASCO 2023 POSTER

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

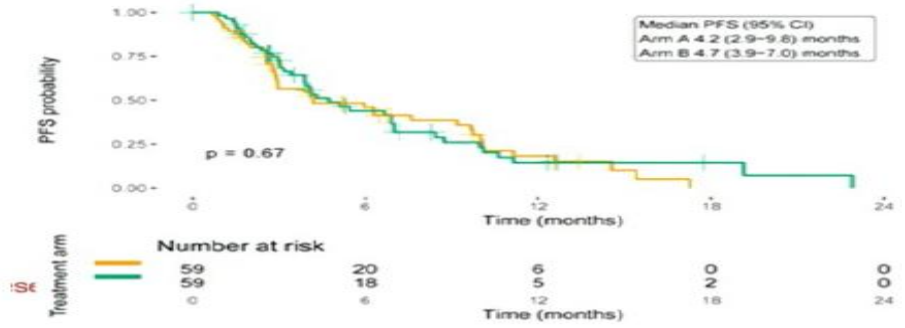
Study Design – The NIPU trial, a phase II study

*Treatment beyond progression permitted when evidence of clinical bene

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, Aus

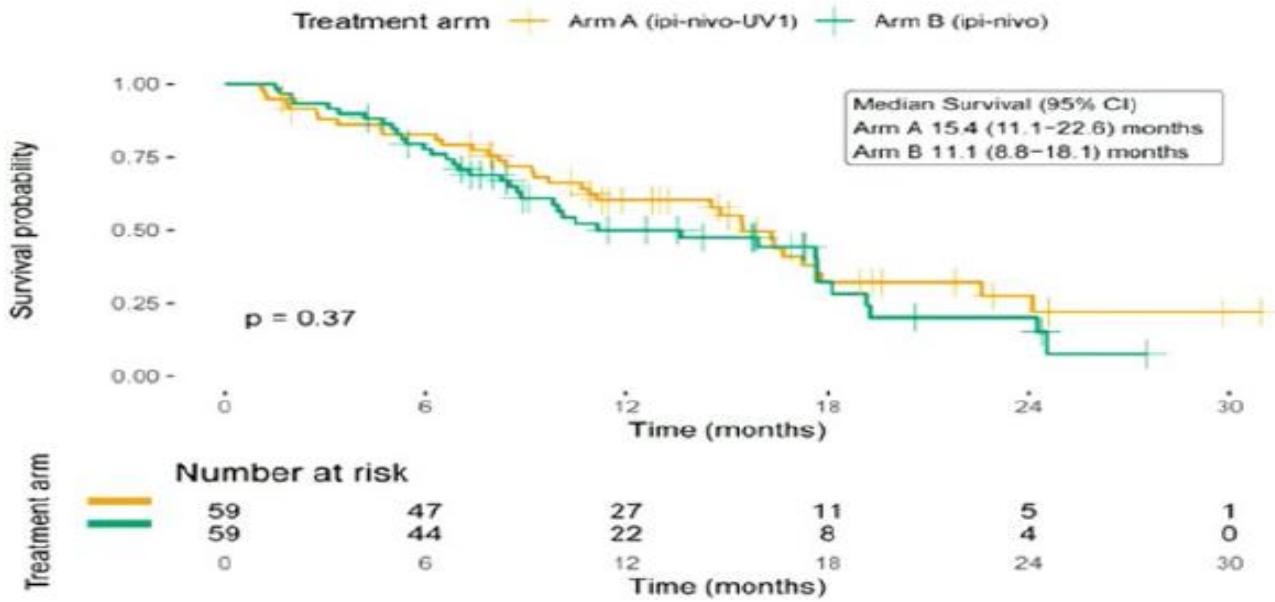
Primary endpoint	Secondary endpoints	Exploratory endpoints
• PFS by mRECIST, BICR	• OS, ORR, DCR • QoL • Toxicity	• Biomarker analyses

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



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)

Overall survival (17.3 months median follow-up)
Kaplan-Meier plot with logrank test



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)	

#8511: Bemcentinib and pembrolizumab in patients with relapsed mesothelioma: MIST3, a phase IIa trial with cellular and molecular correlates of efficacy

Matthew G Krebs, Amy Branson, Shaun Barber, Charlotte Poile, Amy King, Alastair Greystoke, Sam Moody, Luke Nolan, Molly Scotland, Liz Darlison, Amrita Bajaj, Bruno Morgan, Cassandra Brookes, Peter Wells-Jordan, Catherine Jane Richards, Anne L. Thomas, Dean Anthony Fennell

Key inclusion criteria

- Histologically confirmed pleural mesothelioma
- ECOG PS 0-1
- Prior platinum-based systemic therapy (max 2 lines)
- Measurable disease by mRECIST1.1
- Adequate hematological and biochemical status
- Willingness to undergo a fresh biopsy (optional)

Pre-treatment biopsy

Treatment

- Bemcentinib 400mg po for 3 days then 200mg OD every 3 weeks
- Pembrolizumab 200mg IV every 3 weeks

Treatment until disease progression

Re-biopsy on progression

Correlative Research

- Baseline and relapsed DNA and RNA sequencing
- Gut 16s RNA sequencing
- Tissue microarray & ultradeep multiplex immunofluorescence
- AXL IHC and sAXL

Primary endpoint:

Disease control rate at 12 weeks (DCR12w).*

Secondary endpoints:

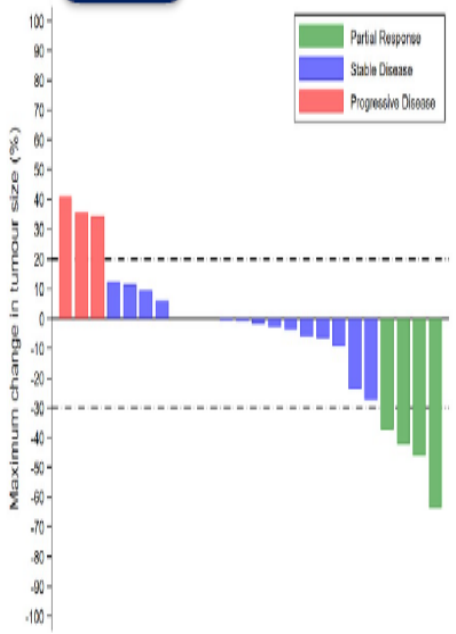
DCR at 24 weeks (DCR24w),

Best objective response rate (ORR) and toxicity (NCI CTCAE 4.03).

Characteristic (n=26)		N (%)
Age (years)	Median (range)	73 (55-85)
Gender	Male	23 (88.5)
	Female	3 (11.5)
Mesothelioma subtype	Epithelioid	23 (88.5)
	Biphasic	2 (7.7)
	Sarcomatoid	1 (3.8)
History of asbestos	Yes	20 (76.9)
	Unknown	6 (23.1)
ECOG status	0	6 (23.1)
	1	20 (76.9)
Metastases	No	19 (73.1)
	Yes	7 (26.9)
Primary tumour site	Thoracic	25 (96.2)
	Missing	1 (3.8)

*minimum 11/26 patients with DCR needed to meet threshold for further evaluation

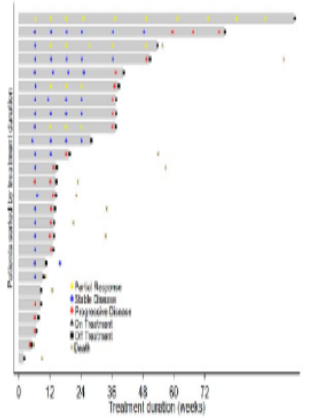
Efficacy



Waterfall plot of best responses of patient within 24 weeks (N = 24^)

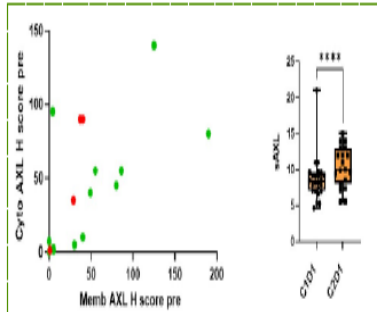
Tumour assessment was not available for two patients

Outcome	n (%)
DCR12weeks	12/26 (46.2%)
DCR24weeks	10/26 (38.5%)
ORR	15.4%
PR	4/26 (15.4%)
CR	0/26 (0%)
SD	15/26 (57.7%)
PD	7/26 (27%)



Safety

ADVERSE EVENT	Total N (%)	G1/2 N(%)	G3 N (%)
Fatigue	12 (46)	11 (42)	1 (4)
Nausea	11 (42)	11 (42)	0 (0)
Diarrhoea	7 (27)	6 (23)	1 (4)
Weight loss	7 (27)	6 (23)	1 (4)
Constipation	6 (23)	6 (23)	0 (0)
Raised creatinine	6 (23)	6 (23)	0 (0)
Anaemia	5 (19)	5 (19)	0 (0)
Increased ALT	5 (19)	5 (19)	0 (0)
Increased AST	5 (19)	5 (19)	0 (0)
Fever	5 (19)	5 (19)	0 (0)
Peripheral oedema	5 (19)	5 (19)	0 (0)



Tumour reduction (Green) vs Growth (Red) as best response

PD biomarker – increase in sAXL on treatment

MiST3 met its primary endpoint por DCR and warrants further evaluation in patients who are refractory or who have relapsed following prior standard chemotherapy

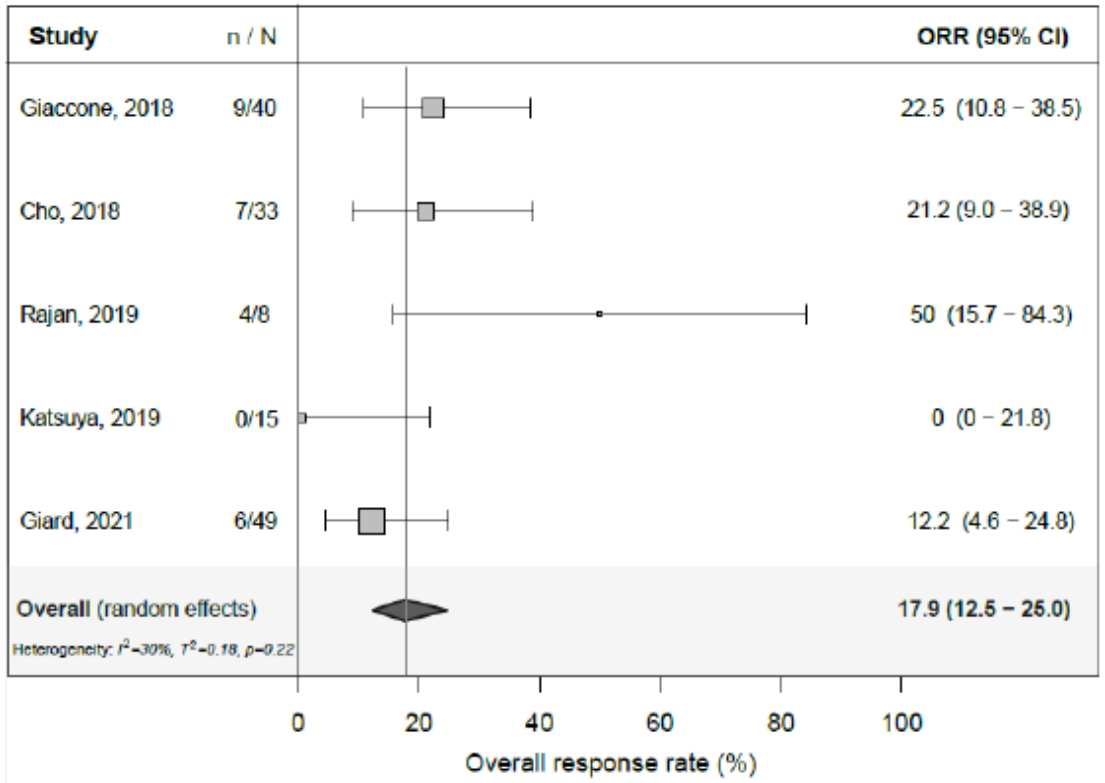
Timoma /ca tímico

Immune checkpoint inhibitors for thymic carcinoma

The efficacy of pembrolizumab, nivolumab, and avelumab has been reported (TC=125)

The response rate of IO for thymic carcinoma was

- 17.9% (95%CI 12.5 – 25.0)
- the DCR was 72.4% (95%CI 64.6 – 79.1) and 1-year survival rate of 65%



Autoimmunity-related irAE

- Gr ≥ 3 AID in 26.9% of TET
- **Gr ≥ 3 AID in thymoma: 71.4%, in thymic ca: 17.1%**
- Gr ≥ 4 liver injury: 3.3% for TET
- Gr ≥ 4 myocardial damage: 4.7%
- Gr 5 was not reported

Villacampa G Eur J Cancer 2023;180:117-124.

Summary: Key drugs for thymoma and thymic carcinoma

Thymoma: 1L. ORR with approximately 60%

- 1L: Cisplatin and Doxorubicin containing chemotherapy
  ADOC, CAP, CAMP, and CODE
- 2L+: Etoposite, Everolimus, Octreotide, pemetrexed,
  Gemcitabine±capecitabine

Thymic carcinoma: 1L. ORR 20-30%, 2L+. ORR 10-40%

- 1L: CBDCA+PTX
- 2L+: Lenvatinib, Pembrolizumab, Nivoluamb, Sunitinib, Pemetrexed, Palbociclib,
  Gemcitabine±capecitabine, and S-1

Thymic NET and NEC:

Treatment according to NET or NEC originating from the GI or lung
(somatostatin analogue (+^{177}Lu), chemo, and everolimus)

GECP
lung cancer research

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

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

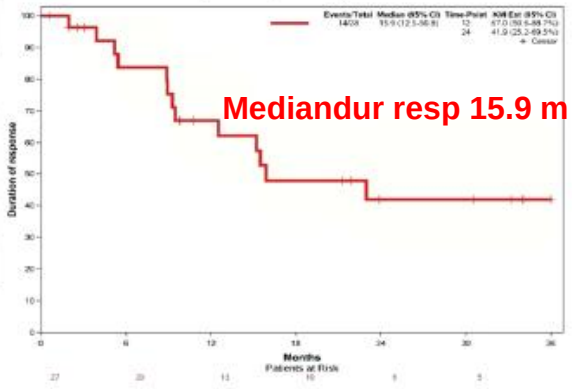
Two-stage Green-Dahlberg statistical plan: The null hypothesis that the true objective response rate (ORR) is 20% (Lemma et al., 2011) had to be tested against a one-sided alternative. In the first stage, 30 patients had to be accrued. If there were 4 or fewer responses in these 30 patients, the study 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

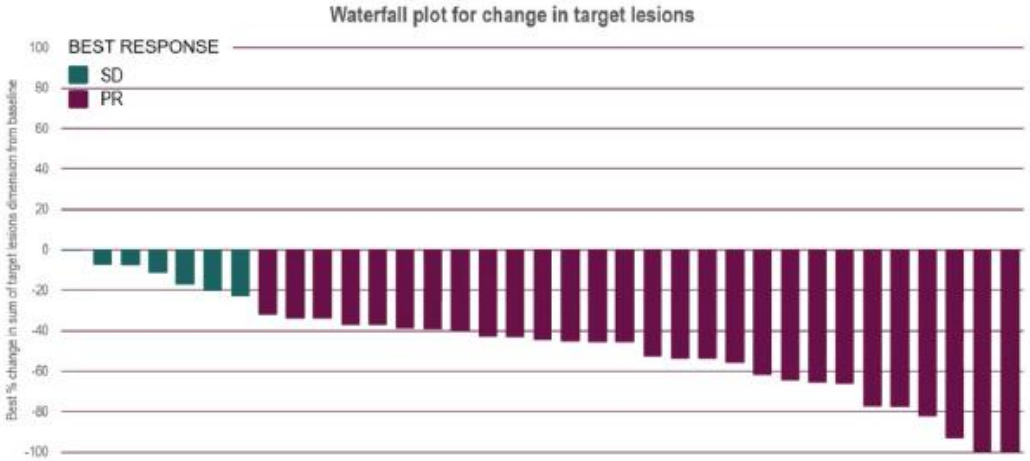
Response evaluated by Investigator	ITT population N=35
ORR - n (%) [95% CI]	28 (80.0) [63.1 - 91.6]
CR	0 (0.0)
PR	28 (80.0)
SD	7 (20.0)
PD	0 (0.0)
DCR - n (%) [95% CI]	35 (100.0) [90.0 – 100.0]

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;

Duration of response (N=28)



Depth of response by Investigator Assessment



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Proto C. ESMO 2023

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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

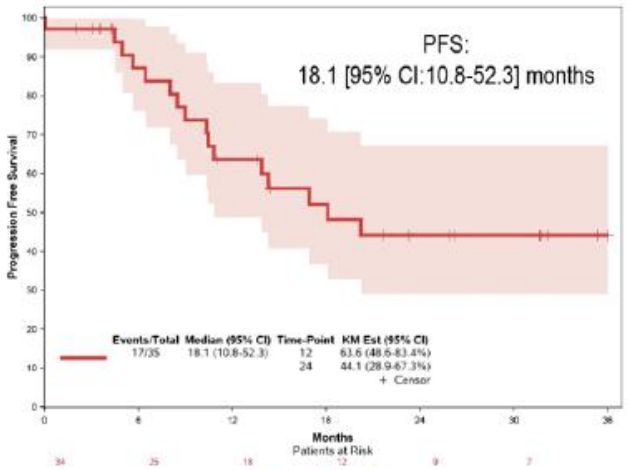
SAE	Grade	Ramucirumab relationship	Outcome
Pulmonary embolism	G4	Yes	Resolved
Arterial haemorrhage	G3	Yes	Resolved
Acute myocardial infarction	G3	Yes	Resolved with sequelae
Acute myocardial infarction	G3	Yes	Resolved

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

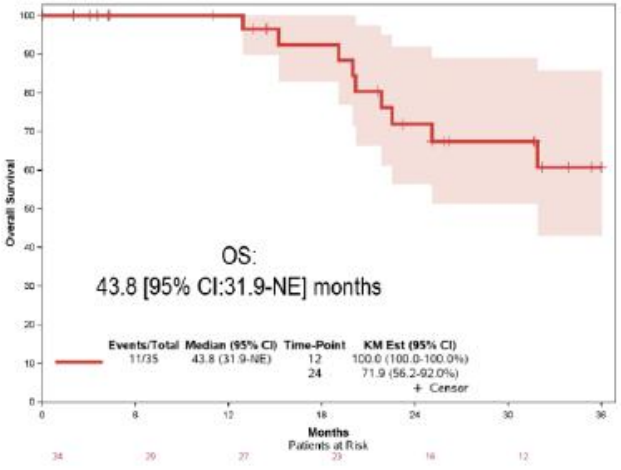
Among the remaining 4 Serious TEAEs, 3 were NDR, 1 was only CT related
All the Serious TEAEs resolved

Efficacy outcomes by Investigator Assessment

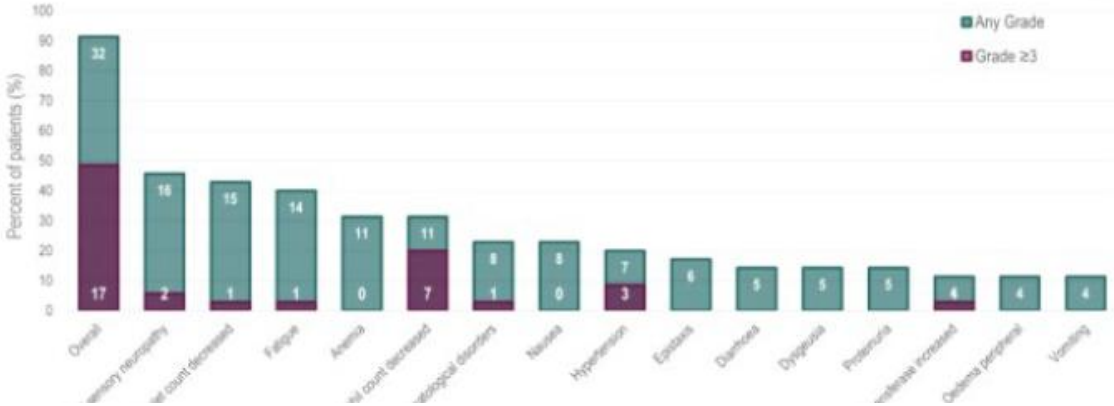
Progression-free Survival (N=35)



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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	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**

Courtesy Manuel Dómine

What's the next game-changer for thymic malignancies?

Strategic/Combo

NCT04554524
Carbo-paclitaxel/Nab-paclitaxel + Pembrolizumab (Phase 4)
2020.8 – 2024.7
China, Thy B3+ TC, n= up to 40
Primary endpoint = ORR

NCT03921671
CBDCA+PTX+Ramucirumab
RELEVENT
2018.11 – 2021.10
Italy, Thy B3+ TC, n=60
Primary endpoint = ORR

jRCT2031220144
CBDCA + PTX + Atezolizumab
JTD2101: Marble
2022.8 – 2024.7
Japan, TC, n= 47
Primary endpoint = ORR

NCT03463460
Pembrolizumab + Sunitinib
2018.12 – 2020.12
Ohio State U. n=40 (thy B3+ TC)
Primary endpoint = ORR

NCT04710628
Pembrolizumab + Lenvatinib
PECATI
2021.4 – 2023.3
France + Spain, n=43 (thy B3+ TC)
Primary endpoint = PFS

NCT05832827
CBDCA + PTX + Pembrolizumab + Lenvatinib
artermis
2023.9 – 2025.9
Japan, TC, n= 35
Primary endpoint = ORR

What's the next game-changer for thymic malignancies?

IND

NCT04469725
KN046
(PD-L1/CTLA4 Bispecific Single Domain Fc Fusion Protein Ab)

2021.6 → 2026.1
n=29, IO post-PD
Primary endpoint = PFS

NCT03193437
Selinexor (KPT-330 and ONO-7705)
oral Selective Inhibitor of Nuclear Export (SINE) compound

2018.4 → 2021.12
Gerogetown U. n = 50 (US=25 + EU=25), thy = 25; TC = 25
Primary endpoint = ORR

NCT044177660
Bintrafusp Alfa (M7824)
PD-1 + TGF-β trap

2020.6 → 2023.4
NCI. n=38
Primary endpoint = ORR

NCT05104736
PT-112
Metallo-pyrophosphate conjugate

2022.4 → 2025.6
NCI sponsored n = 53
Primary endpoint = ORR