Lung Cancer UPDATES
WCLC HIGHLIGHTS
06 - 09 SEPTIEMBRE 2025
Barcelona, Spain

Iniciativa científica de:
GECP lung cancer research

Cáncer de pulmón microcítico, mesotelioma y otros tumores

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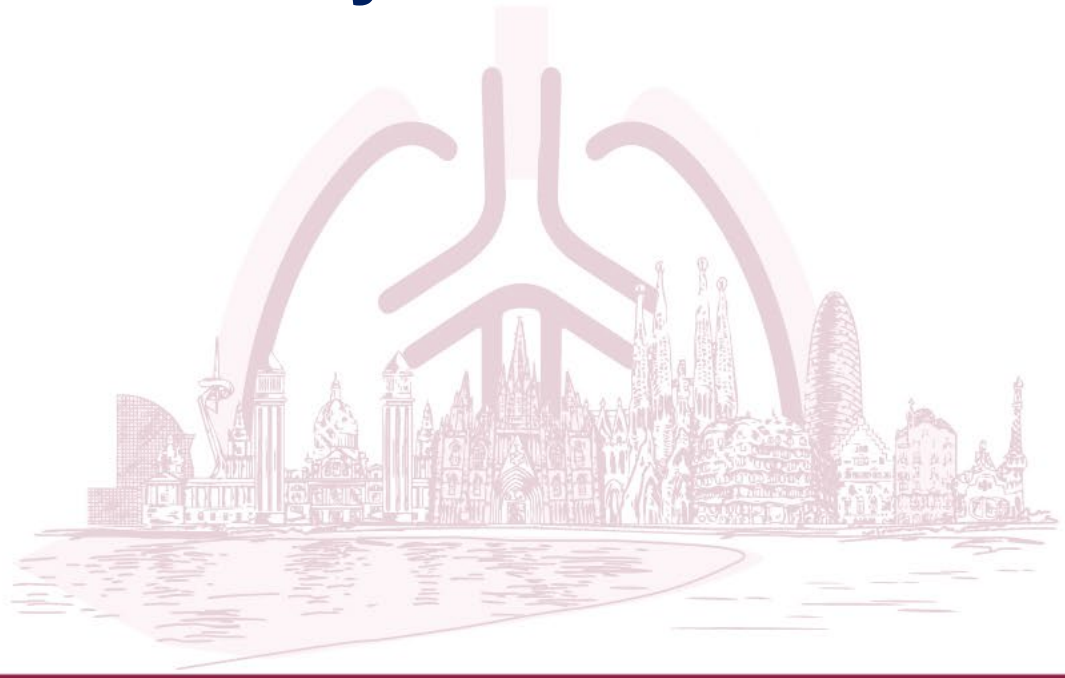
Hospital Universitari Son Espases



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Cáncer de pulmón microcítico - ADC

IASLC 2025 World Conference on Lung Cancer

SEPTEMBER 6-9, 2025 | BARCELONA, SPAIN

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A first-in-human phase 1 study of SHR-4849 (IDE849), a DLL3-directed antibody-drug conjugate, in relapsed SCLC

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Background

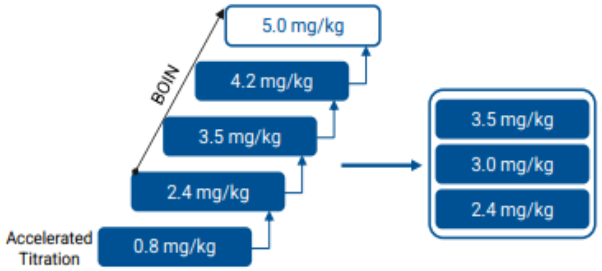
- **Small Cell Lung Cancer (SCLC)** is a highly aggressive neuroendocrine carcinoma (NEC), with limited treatment options and poor prognosis in the second-line setting.
- **Delta-like ligand 3 (DLL3),** a protein that inhibits Notch signaling, is highly expressed in SCLC and other NECs.[1-4]
- **SHR-4849 (IDE849*)** is an antibody-drug conjugate comprising a humanized anti-DLL3 IgG1 monoclonal antibody, linked to a DNA topoisomerase I inhibitor payload by a cleavable linker.
- In preclinical studies,[5] SHR-4849:
  - Strongly inhibited the proliferation of human lung cancer cell lines with different DLL3 expression level;
  - Demonstrated a robust bystander killing effect;
  - Resulted in a dramatic and sustained inhibition of tumor growth in DLL3 expressing xenograft models.

Study design

- A multicenter, open-label phase 1 study of SHR-4849 in advanced solid tumors (ClinicalTrials.gov, NCT06443489).

Key eligibility criteria

- Histologically or cytologically confirmed relapsed or metastatic SCLC and other NECs expressing DLL3;
- Had progressive or recurrent disease after standard treatment(s);
- ECOG PS of 0 or 1.



SHR-4849 was administered intravenously every 3 weeks.

Primary endpoints:
- Safety;
- MTD or MAD;
- RP2D.

Secondary endpoints:
- Efficacy;
- Pharmacokinetics;
- Immunogenicity.

Data cutoff: Jun 20, 2025

- During dose escalation, 1 DLT (grade 4 decreased platelet count) occurred at 4.2 mg/kg.
- 2.4, 3.0, and 3.5 mg/kg SHR-4849 every 3 weeks were selected for further expansion.
- Overall, 100 patients were treated: 0.8 mg/kg (N=1), 2.4 mg/kg (N=25), 3.0 mg/kg (N=29), 3.5 mg/kg (N=42), 4.2 mg/kg (N=3).
- The median follow-up duration was 3.5 months (IQR, 1.4-5.8).

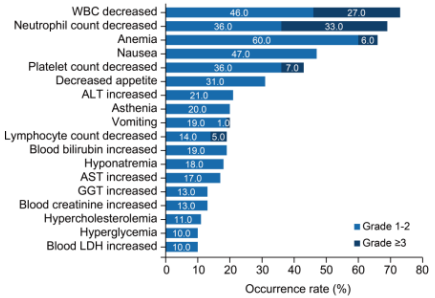
Safety profile

Summary

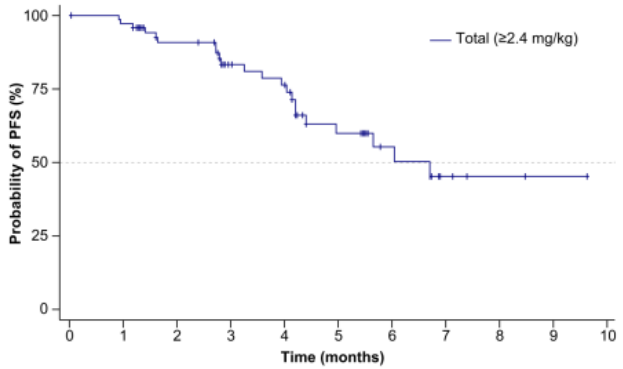
	Total (N=100)
Any TEAE	92 (92.0%)
Grade ≥3	52 (52.0%)
Any TRAE	92 (92.0%)
Grade ≥3	48 (48.0%)
Leading to dose reduction	15 (15.0%)
Leading to treatment discontinuation	2 (2.0%)
Serious	16 (16.0%)
Leading to death	0

Data are n (%).

TRAEs occurring in ≥10% of patients

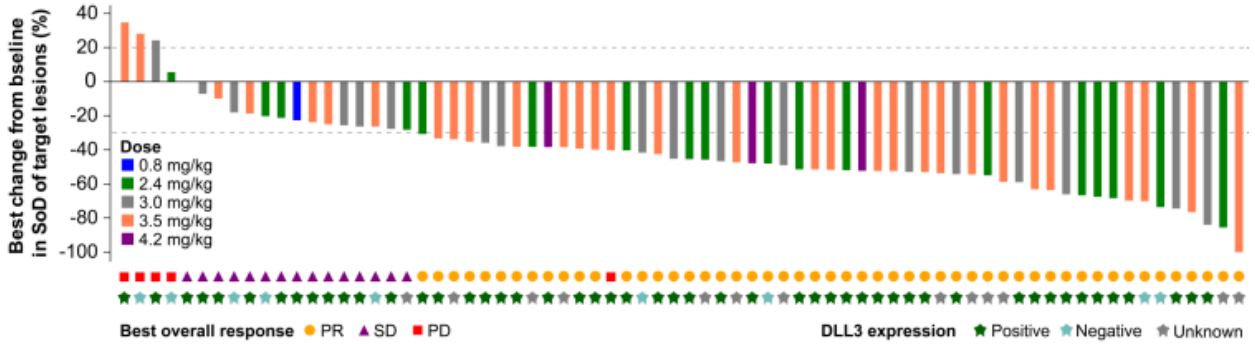


PFS in SCLC



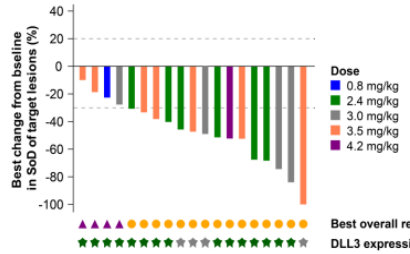
	Total (≥2.4 mg/kg)	
	2L Setting (n=42)	All (n=86)
Events, n (%)	8 (19.0%)	22 (25.6%)
Median (95% CI), months	NR (4.4-NR)	6.7 (4.4-NR)
3-month rate, % (95% CI)	93.3% (75.2-98.3)	83.3% (71.0-90.7)
6-month rate, % (95% CI)	59.0% (31.2-78.8)	55.3% (37.8-69.7)

Tumor response in SCLC



	2.4 mg/kg		3.0 mg/kg		3.5 mg/kg		4.2 mg/kg		Total (≥2.4 mg/kg)	
	2L Setting (n=10)	All (n=19)	2L Setting (n=8)	All (n=18)	2L Setting (n=16)	All (n=31)	2L Setting (n=1)	All (n=3)	2L Setting (n=35)	All (n=71)
ORR, n (%; 95% CI)	8 (80.0%; 44.4-97.5)	14 (73.7%; 48.8-90.9)	6 (75.0%; 34.9-96.8)	12 (66.7%; 41.0-86.7)	12 (75.0%; 47.6-92.7)	23 (74.2%; 55.4-88.1)	1 (100.0%; 2.5-100.0)	3 (100.0%; 29.2-100.0)	27 (77.1%; 59.9-89.6)	52 (73.2%; 61.4-83.1)
Confirmed ORR, n (%; 95% CI)	7 (70.0%; 34.8-93.3)	11 (57.9%; 33.5-79.7)	2 (25.0%; 3.2-65.1)	4 (22.2%; 6.4-47.6)	11 (68.8%; 41.3-89.0)	16 (51.6%; 33.1-69.8)	1 (100.0%; 2.5-100.0)	3 (100.0%; 29.2-100.0)	21 (60.0%; 42.1-76.1)	34 (47.9%; 35.9-60.1)
Response pending confirmation, n (%)	0	1 (5.3%)	4 (50.0%)	8 (44.4%)	0	1 (3.2%)	0	0	4 (11.4%)	10 (14.1%)
DCR, n (%; 95% CI)	10 (100.0%; 69.2-100.0)	18 (94.7%; 74.0-99.9)	8 (100.0%; 63.1-100.0)	17 (94.4%; 72.7-99.9)	15 (93.8%; 69.8-99.8)	28 (90.3%; 74.2-98.0)	1 (100.0%; 2.5-100.0)	3 (100.0%; 29.2-100.0)	34 (97.1%; 85.1-99.9)	66 (93.0% 84.3-97.7)

Tumor response in SCLC with brain metastases



	2.4 mg/kg (n=6)	3.0 mg/kg (n=4)	3.5 mg/kg (n=7)	4.2 mg/kg (n=1)	Total (≥2.4 mg/kg) (n=18)
ORR, n (%; 95% CI)	6 (100.0%; 54.1-100.0)	3 (75.0%; 19.4-99.4)	5 (71.4%; 29.0-96.3)	1 (100.0%; 2.5-100.0)	15 (83.3%; 58.6-96.4)
Confirmed ORR, n (%; 95% CI)	5 (83.3%; 35.9-99.6)	2 (50.0%; 6.8-93.2)	4 (57.1%; 18.4-90.1)	1 (100.0%; 2.5-100.0)	12 (66.7%; 41.0-86.7)
Response pending confirmation, n (%)	0	1 (25.0%)	0	0	1 (5.6%)
DCR, n (%; 95% CI)	6 (100.0%; 54.1-100.0)	4 (100.0%; 39.8-100.0)	7 (100.0%; 59.0-100.0)	1 (100.0%; 2.5-100.0)	18 (100.0%; 81.5-100.0)

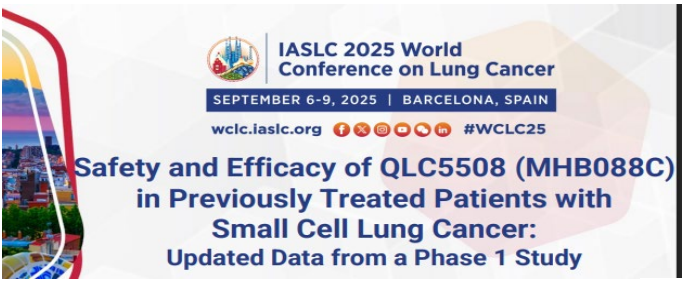
GECP lung cancer research

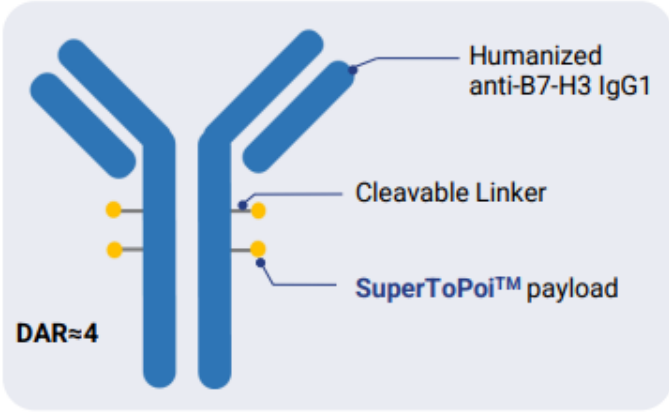
Conclusions

- **SHR-4849 (IDE849) demonstrated a tolerable and manageable safety profile in patients with relapsed SCLC.**
  - Common grade 3 or 4 TRAEs were hematological toxicities;
  - Low incidence of TRAEs leading to treatment discontinuation (2.0%);
  - No treatment-related deaths.
- **SHR-4849 at ≥2.4 mg/kg exhibited promising anti-tumor activity, especially in the second-line setting.**
  - All settings: ORR, 73.2%; DCR, 93.0%;
  - Second-line setting: ORR, 77.1%; DCR, 97.1%;
  - Patients with brain metastases: ORR, 83.3%; DCR, 100.0%.
- **Follow-up is ongoing to assess the long-term outcomes.**

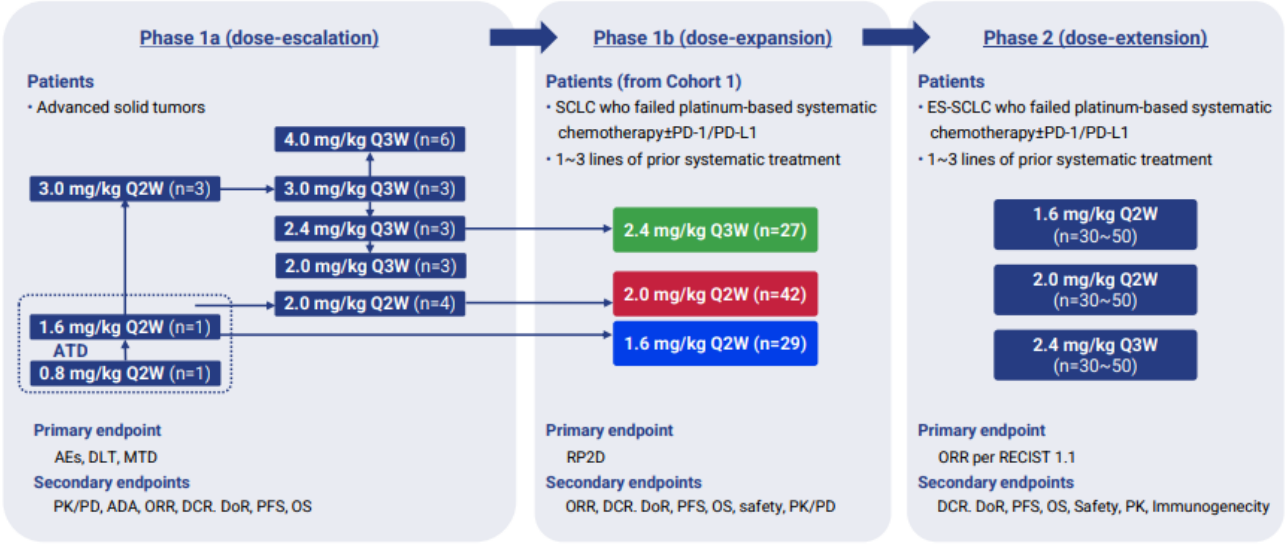
Introduction

- ES-SCLC accounts for 70% of total patients with SCLC. Second-line therapy for patients with ES-SCLC includes lurbinectedin (ORR 35%, mPFS 3.7 months) and tarlatamab (ORR 40%, mPFS 4.9 months).[1]
- QLC5508 (MHB088C), a novel B7-H3-targeted ADC with high cell-binding activity and internalization rate, contains SuperTopoi™ payload which is 5 to 10 times more potent than Dxd.
- The preliminary data of a phase 1 study indicated the promising anti-tumor activity and tolerability of QLC5508 in patients with solid tumors, including ES-SCLC.[2]
- Here we report the updated results of survival and safety in patients with ES-SCLC.





Study design



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Safety profile

- TRAEs of ≥grade 3 occurred in 15 (50.0%), 16 (34.8%), and 13 (43.3%) patients in 1.6 mg/kg Q2W, 2.0 mg/kg Q2W, and 2.4 mg/kg Q3W cohorts, respectively.
- Two (4.3%) patients discontinued the treatment due to TRAEs of grade 2/3 ILD (both in 2.0 mg/kg Q2W cohort and finally recovered).
- No TRAEs leading to death occurred.

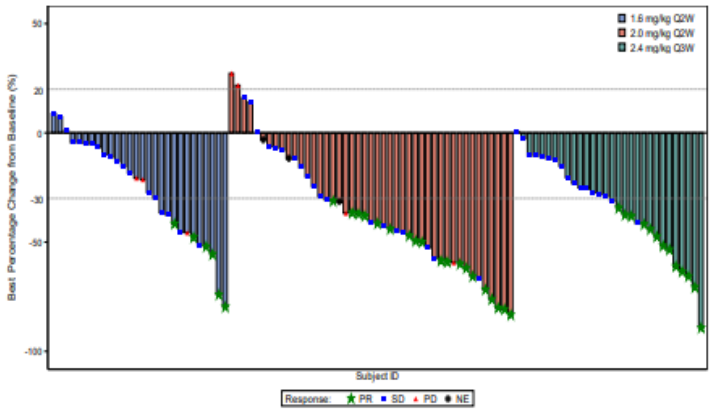
TRAEs, n (%)	1.6 mg/kg Q2W (N=30)	2.0 mg/kg Q2W (N=46)	2.4 mg/kg Q3W (N=30)	Total (N=106)
TRAEs of any grade	30 (100.0)	45 (97.8)	30 (100.0)	105 (99.1)
TRAEs of ≥grade 3	15 (50.0)	16 (34.8)	13 (43.3)	44 (41.5)
TRSAEs	10 (33.3)	5 (10.9)	3 (10.0)	18 (17.0)
TRAEs leading to treatment discontinuation	0	2 (4.3)	0	2 (1.9)
TRAEs leading to dose interruption	9 (30.0)	12 (26.1)	5 (16.7)	26 (24.5)
TRAEs leading to death*	0	0	0	0
Infusion-related reaction	7 (23.3)	13 (28.3)	10 (33.3)	30 (28.3)

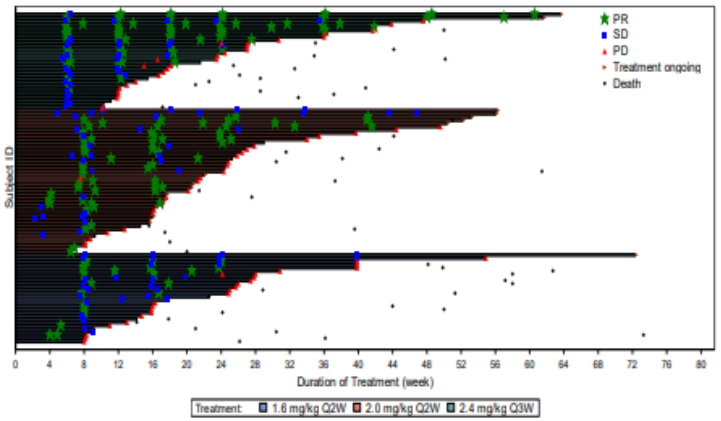
*One patient (3.3%) died due to cachexia in the 1.6 mg/kg cohort, which was considered unrelated to the treatment.

TRAEs

- Grade ≥3 TRAEs (>10% in all patients) were neutrophil count decreased (17.0%) and WBC count decreased (10.4%).
- Grade ≥3 TRAEs (>10%) were anemia (10.9%) in 2.0 mg/kg Q2W cohort and were neutrophil count decreased (40.0%) and WBC count decreased (20.0%) in 2.4 mg/kg Q3W cohort.

Anti-tumor activity

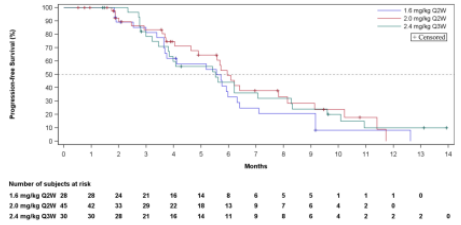


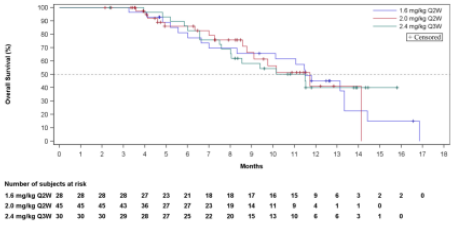


Data cut-off date: Jun 13, 2025

Anti-tumor activity in the efficacy set	1.6 mg/kg Q2W (N=28)	2.0 mg/kg Q2W (N=45)	2.4 mg/kg Q3W (N=30)	Total (N=103)
Confirmed ORR, % (95% CI)	21.4 (8.3-41.0)	42.2 (27.7-57.8)	43.3 (25.5-62.6)	36.9 (27.6-47.0)
DCR, % (95% CI)	89.3 (71.8-97.7)	84.4 (70.5-93.5)	100 (88.4-100)	90.3 (82.9-95.2)
Median DoR (95% CI), months	4.22 (3.75-NE)	4.47 (3.91-9.46)	7.00 (4.14-NE)	5.82 (4.21-7.36)

Survival outcomes





Data cut-off date: Jun 13, 2025

Survival outcomes in the efficacy set	1.6 mg/kg Q2W (N=28)	2.0 mg/kg Q2W (N=45)	2.4 mg/kg Q3W (N=30)	Total (N=103)
Median PFS (95% CI), months	5.55 (3.65-6.31)	5.95 (4.63-8.15)	5.52 (3.81-7.06)	5.72 (4.63-6.21)
Median OS (95% CI), months	11.50 (7.00-13.34)	11.73 (8.77-NE)	11.50 (7.59-NE)	11.50 (9.40-13.34)

Conclusion

- QLC5508 showed **manageable and tolerable safety** profile.
  - Two (4.3%) patients discontinued the treatment due to TRAEs of interstitial lung disease (both in 2.0 mg/kg Q2W dose level).
  - Grade ≥3 TRAEs (>10% in all patients with SCLC) were neutrophil count decreased (17.0%) and WBC count decreased (10.4%).
  - No treatment-related death occurred.
- QLC5508 showed **prolonged survival** in previously treated patients with ES-SCLC.
  - Median PFS: 5.72 months in all efficacy-evaluable patients with ES-SCLC, **5.95 months** at 2.0 mg/kg Q2W dose level.
  - Median OS: 11.50 months in all efficacy-evaluable patients with ES-SCLC, **11.73 months** at 2.0 mg/kg Q2W dose level.
- QLC5508 **2.0 mg/kg Q2W** is being evaluated in an ongoing phase 3 study.

Abbreviations: TRAEs, treatment-related adverse events; WBC, white blood cell; ES-SCLC, extensive-stage small cell lung cancer; PFS, progression-free survival; OS, overall survival.

Ifinatamab Deruxtecan (I-DXd) in Extensive-Stage Small Cell Lung Cancer: Primary Analysis of the Phase 2 IDeate-Lung01 Study

Myung-Ju Ahn,[1] Melissa L. Johnson,[2] Luis Paz-Ares,[3] Makoto Nishio,[4] Christine L. Hann,[5] Nicolas Girard,[6] Pedro Rocha,[7] Hidetoshi Hayashi,[8] Tetsuya Sakai,[9] Yu Jung Kim,[10] Haichuan Hu,[11] Meng Qian,[12] Jasmeet Singh,[12] Juliette Godard,[13] Mei Tang,[12] Charles M. Rudin[14]

Introduction

- Despite recent advancements in treatment options beyond 1L for patients with ES-SCLC, outcomes remain poor, and there is still no globally accepted standard of care[1–5]
- I-DXd is a B7-H3–directed ADC designed to enhance selective tumor-cell death and reduce systemic exposure, comprising[6–9]:
  - A humanized anti–B7-H3 IgG1 mAb
  - A tetrapeptide-based cleavable linker that covalently bonds antibody and payload
  - A TOPO I inhibitor payload (an exatecan derivative, DXd)
- IDeate-Lung01 is a Phase 2, two-part trial (Part 1: dose optimization; Part 2: extension) designed to evaluate the efficacy and safety of I-DXd at doses of 8 and 12 mg/kg Q3W in previously treated ES-SCLC
  - Based on the overall benefit–risk assessment using pooled data from the interim analysis of Part 1 of IDeate-Lung01 and the Phase 1/2 trial,[10] the 12-mg/kg dose was selected for further investigation in Part 2

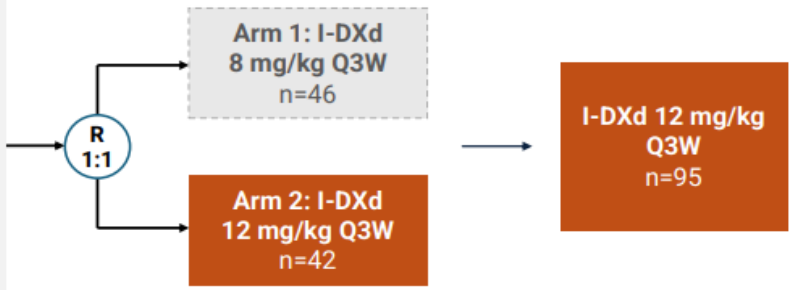
We present data from the primary analysis of IDeate-Lung01, with a focus on patients treated with I-DXd 12 mg/kg across both parts of the study

IDeate-Lung01 study design

Phase 2, multicenter, randomized, open-label study (NCT05280470)

Patient eligibility

- Histologically or cytologically documented ES-SCLC
- Age ≥18 years[a]
- ≥1 prior line of PBC and ≤3 prior lines of systemic therapy
- Radiologically documented PD on or after most recent prior systemic therapy
- ECOG PS 0–1
- ≥1 measurable lesion per RECIST 1.1[b]
- Patients with asymptomatic brain metastases (untreated or previously treated) were eligible



Stratification factors:

- 2L CTFI <90 days; 2L CTFI ≥90 days; 3L or 4L
- Prior anti–PD-(L)1 treatment (yes or no)

Primary endpoint

- ORR by BICR[c]

Secondary endpoints

- DOR by BICR and inv[c]
- PFS by BICR and inv[c]
- OS
- DCR by BICR and inv[c]
- TTR by BICR and inv[c]
- ORR by inv[c]
- Safety
- Pharmacokinetics
- Immunogenicity

Exploratory analysis

- Intracranial ORR by BICR[d]

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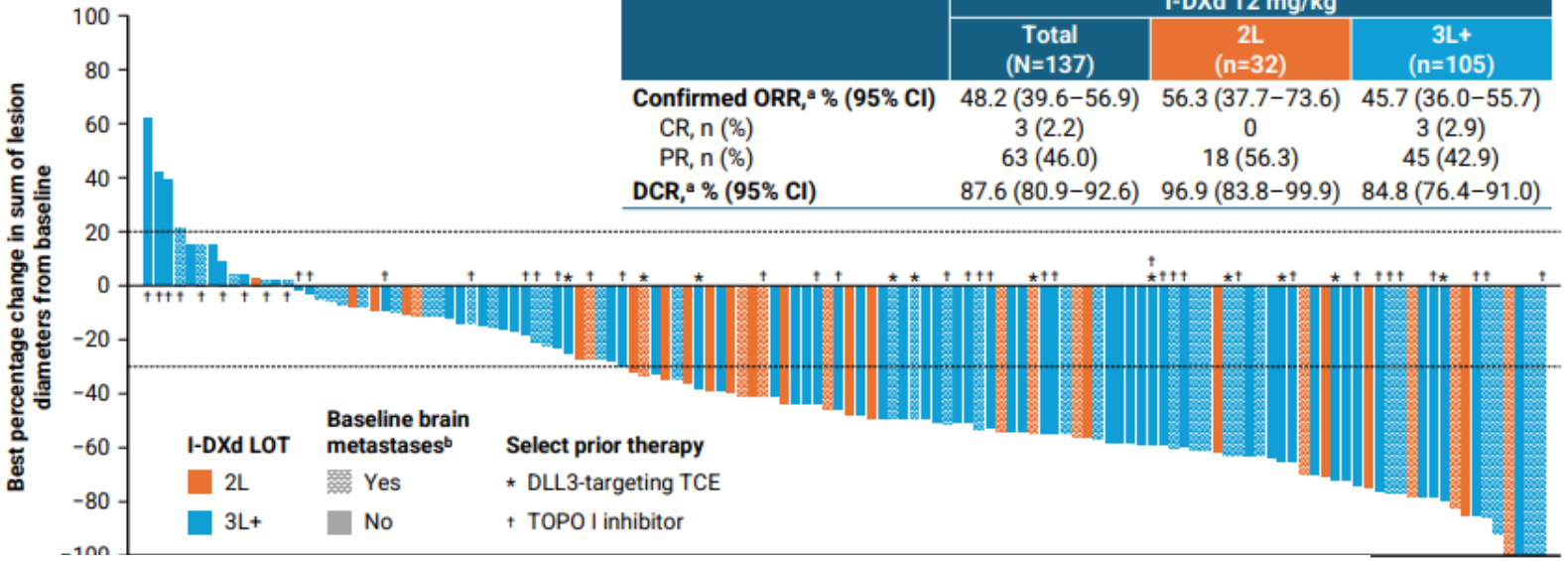
I-DXd 12 mg/kg demonstrated promising antitumor activity

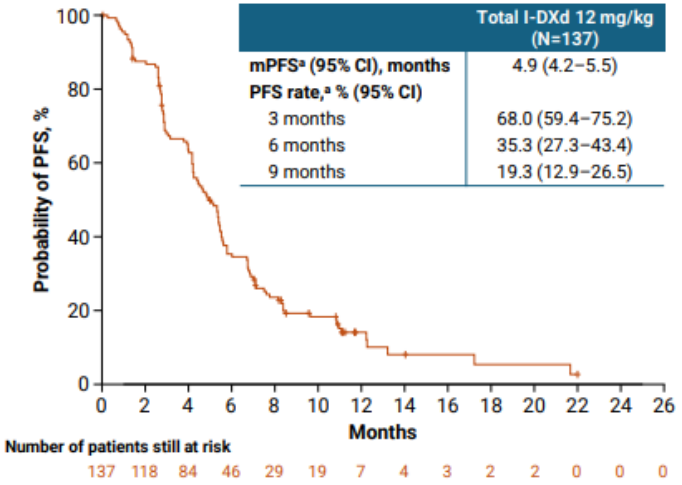
	I-DXd 12 mg/kg		
	Total (N=137)	2L (n=32)	3L+ (n=105)
Confirmed ORR,[a] % (95% CI)	48.2 (39.6–56.9)	56.3 (37.7–73.6)	45.7 (36.0–55.7)
CR, n (%)	3 (2.2)	0	3 (2.9)
PR, n (%)	63 (46.0)	18 (56.3)	45 (42.9)
DCR,[a] % (95% CI)	87.6 (80.9–92.6)	96.9 (83.8–99.9)	84.8 (76.4–91.0)



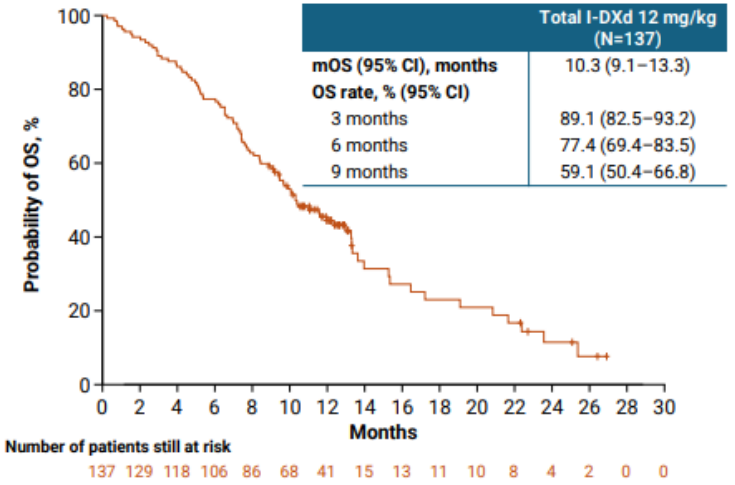
	Total I-DXd 12 mg/kg (N=137; 66 with confirmed CR/PR)
TTR,[a,b] median (range), months	1.4 (1.0–8.1)
DOR,[a,b] median (95% CI), months	5.3 (4.0–6.5)

mPFS was 4.9 months and mOS was 10.3 months with I-DXd 12 mg/kg

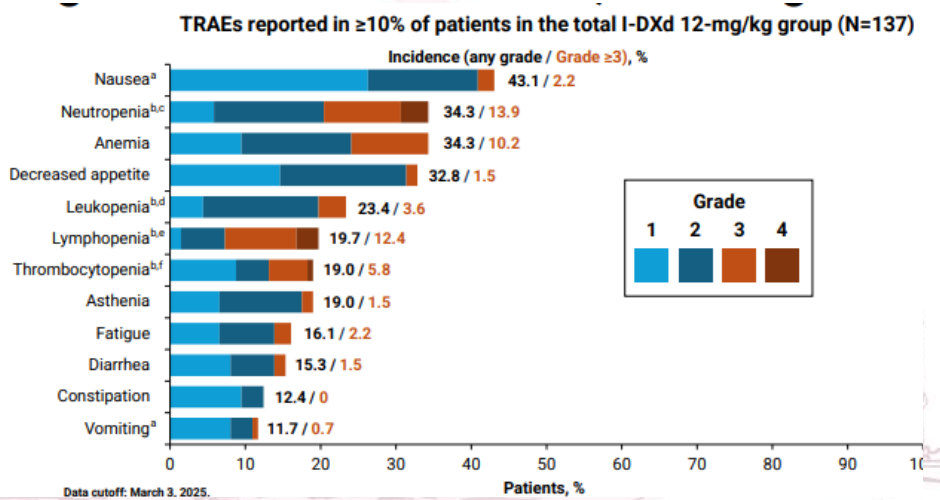
	Total I-DXd 12 mg/kg (N=137)
mPFS[a] (95% CI), months	4.9 (4.2–5.5)
PFS rate,[a] % (95% CI)	
3 months	68.0 (59.4–75.2)
6 months	35.3 (27.3–43.4)
9 months	19.3 (12.9–26.5)



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



Among patients who received I-DXd 12 mg/kg as 2L therapy (n=32), mPFS was 5.6 months (95% CI, 3.9–8.1) and mOS was 12.0 months (95% CI, 7.3–19.1)



Conclusions

- I-DXd 12 mg/kg demonstrated remarkable efficacy in patients with previously treated ES-SCLC, particularly given the inclusion of populations often excluded from clinical trials
  - 18/137 with CTFI ≤30 days; 52/137 with asymptomatic untreated or previously treated brain metastases[a]
- Confirmed ORR was 48.2%, median DOR was 5.3 months, median PFS was 4.9 months, and median OS was 10.3 months
- Clinically meaningful benefit was observed regardless of platinum sensitivity or LOT, with confirmed ORRs of:
  - 55.6% (CTFI ≥90 days) and 50.0% (CTFI >30 to <90 days)
  - 56.3% (2L) and 45.7% (3L+)
- Meaningful intracranial efficacy was observed; a full subgroup analysis of patients with baseline brain metastases will be presented at ESMO 2025 (Abstract 2760MO)
- The safety profile of I-DXd 12 mg/kg was manageable and consistent with previous reports[1–3]
- The ongoing global Phase 3 IDeate-Lung02 trial (NCT06203210) is comparing I-DXd 12 mg/kg vs treatment of physician's choice (topotecan, amrubicin, or lurbinectedin) in patients with relapsed SCLC with only 1 prior line of systemic treatment, which must have included PBC

Data cutoff: March 3, 2025.

[a]By BICR.

2L, second-line; 3L+, third-line and beyond; BICR, blinded independent central review; CTFI, chemotherapy-free interval; DOR, duration of response; (ES)-SCLC, (extensive-stage) small cell lung cancer; LOT, line of therapy; ORR, objective response rate; OS, overall survival; PBC, platinum-based chemotherapy; PFS, progression-free survival.

1. Johnson M, et al. Oral presentation at the 2023 IASLC World Conference on Lung Cancer. September 9–12, 2023; Singapore. Presentation OA05.05. 2. Patel MR, et al. Poster presentation at the European Society for Medical Oncology Congress 2023. October 20–24, 2023; Madrid, Spain. Presentation 690P. 3. Rudin CM, et al. Oral presentation at the 2024 IASLC World Conference on Lung Cancer. September 7–10, 2024; San Diego, CA, USA. Presentation OA04.03.

Safety and Efficacy of ABBV-706, a Seizure-Related Homolog Protein 6–Targeting Antibody-Drug Conjugate, in R/R SCLC

ABBV-706

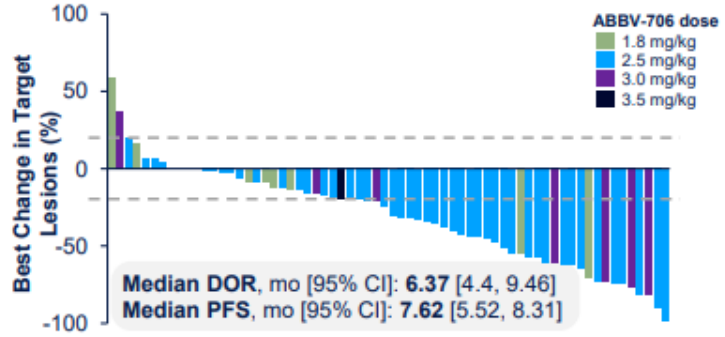
SEZ6 is a specific neuroendocrine lineage marker

- Type I transmembrane protein and neuroendocrine lineage marker[1] is specifically and highly expressed in SCLC[2]

Preliminary phase 1 FIH study (NCT05599984) results

- Encouraging efficacy and manageable safety of ABBV-706 monotherapy in patients with SCLC and NECs[3,4]
- **We present updated SCLC data from randomized dose optimization**

Change in Target Lesion Size by Dose (NECs, N=65)[4]



Phase 1 dose escalation and dose optimization study M23-385 (NCT05599984)

Patient Eligibility

- Histologically or cytologically documented ES-SCLC
- Adults ≥18 years old
- ≥1 prior line with at least 1 platinum-based chemotherapy regimen
- ECOG PS 0–1
- ≥1 measurable lesion per RECIST v1.1
- Patients with prior treated or untreated stable brain metastases were eligible
- Prior exposure to SEZ6-targeted ADCs or ADCs with Top1i payload was not permitted

Dose Escalation

Doses
1.3–3.5 mg/kg (N=60)

Tumor Types
ES-SCLC, high-grade NENs, CNS tumors

1:1

Dose Optimization (SCLC)

ABBV-706 1.8 mg/kg (n=41)

ABBV-706 2.5 mg/kg (n=39)

IV Q3W in 21-day cycles until disease progression or unacceptable toxicity

Primary Objectives and Endpoints

- Safety and tolerability
- PK
- RP2D

Antitumor Activity Endpoints

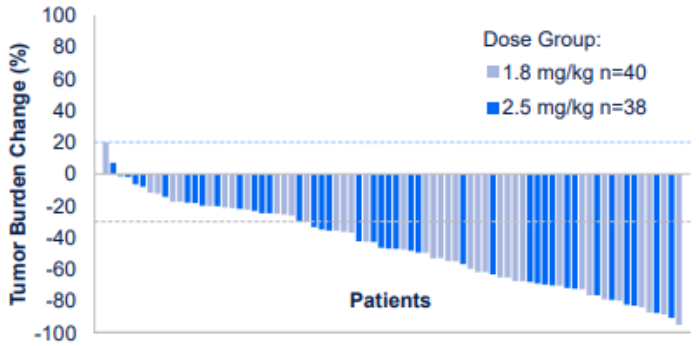
- ORR by Inv
- DOR by Inv
- PFS by Inv
- OS
- Clinical benefit

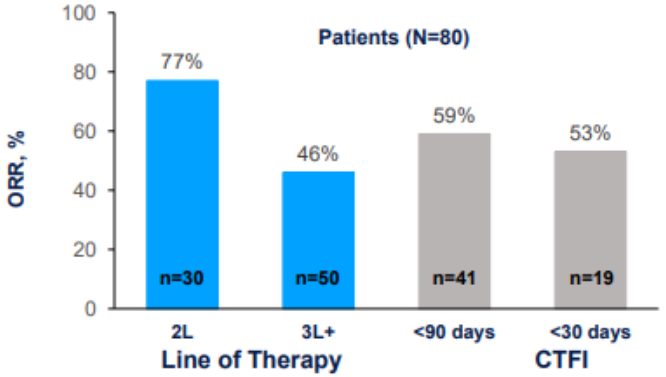
Exploratory Analysis

- SEZ6 by IHC
- Pharmacodynamic and predictive biomarkers

OA06.04

Similar high ORR[a] observed at 1.8-mg/kg and 2.5-mg/kg doses





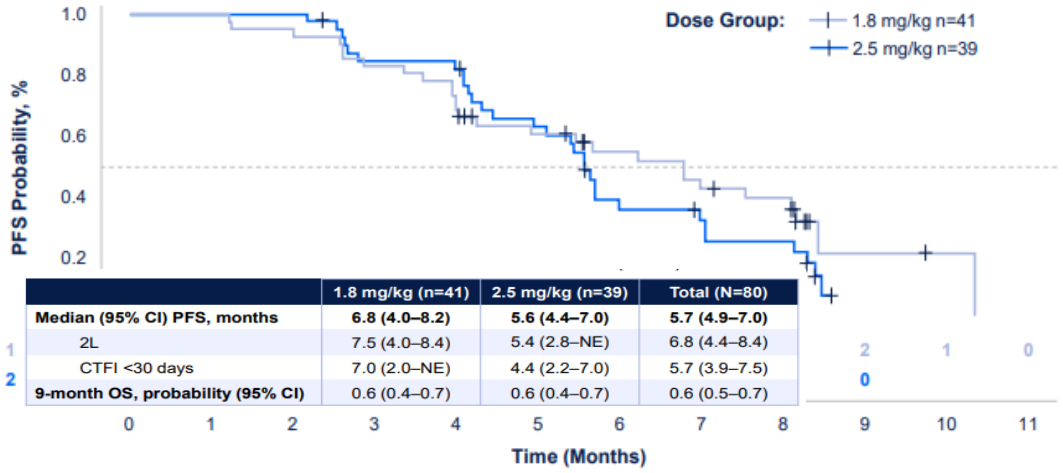
ORR	1.8 mg/kg (n=41)	2.5 mg/kg (n=39)	Total (N=80)
ORR [confirmed CR/PR] (%)	23 (56)	23 (59)	46 (58)
ORR [confirmed CR/PR] by LOT (%)			
2L	13/16 (81)	10/14 (71)	23/30 (77)
3L+	10/25 (40)	13/25 (52)	23/50 (46)
ORR (confirmed CR/PR) by CTFI			
≥90 days	7/12 (58)	10/18 (56)	17/30 (57)
<90 days	13/24 (54)	11/17 (65)	24/41 (59)
<30 days	5/11 (46)	5/8 (63)	10/19 (53)
ORR (confirmed CR/PR) by brain metastases			
Yes	10/16 (63)	6/12 (50)	16/28 (57)
No	10/16 (63)	15/20 (75)	25/36 (69)

Responses observed across key subgroups and further improved in second line

Similar efficacy (to the overall cohort) is seen in patients with platinum-refractory/resistant disease, and in patients with brain metastases

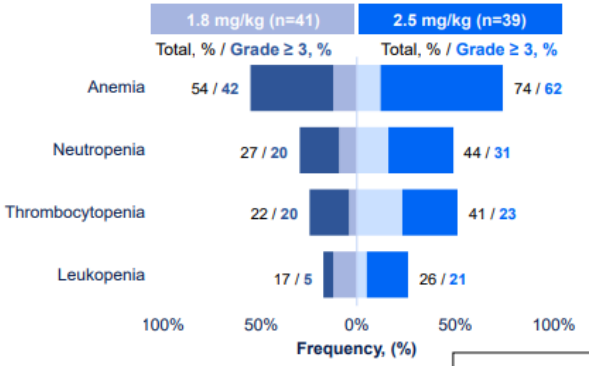
SEZ6 expression is similar between responders and nonresponders

Progression-Free Survival

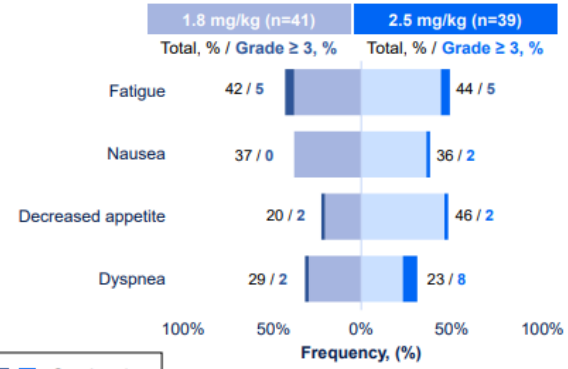


	1.8 mg/kg (n=41)	2.5 mg/kg (n=39)	Total (N=80)
Median (95% CI) PFS, months	**6.8 (4.0–8.2)**	**5.6 (4.4–7.0)**	**5.7 (4.9–7.0)**
2L	7.5 (4.0–8.4)	5.4 (2.8–NE)	6.8 (4.4–8.4)
CTFI <30 days	7.0 (2.0–NE)	4.4 (2.2–7.0)	5.7 (3.9–7.5)
9-month OS, probability (95% CI)	0.6 (0.4–0.7)	0.6 (0.4–0.7)	0.6 (0.5–0.7)

Any Grade Hematologic TEAEs in ≥20% of Patients



Any Grade Non-Hematologic TEAEs in ≥20% of Patients



Conclusions

ABBV-706 has manageable safety and promising efficacy in heavily pretreated patients with R/R SCLC, with most patients receiving durable clinical benefit, including those with platinum-refractory disease

ABBV-706 provides high response rates, quick tumor shrinkage, and rapid symptomatic relief

ABBV-706 efficacy profile in terms of ORR, DOR, and PFS is similar to that of the first-line SOC (platinum-etoposide-CPI) even if given in a later line of treatment

On the basis of totality of the benefit-risk profile, monotherapy RP2D was determined to be 1.8 mg/kg Q3W in SCLC

The authors thank the participants, study sites, and investigators who participated in this clinical trial.

Presenting author: Lauren A. Byers (lbyers@mdanderson.org)

GECP lung cancer research

Key Takeaway

- DLL3- (**SHR-4849**), B7-H3-(**I-DXd** and **QLC 5508**), and SEZ6- (**ABBV-706**) targeted ADCs show promising activity in previously treated ES-SCLC.
- DLL3-targeted ADCs (**SHR-4849**) have preliminary efficacy signals; more mature data are needed.
- Several phase 3 trials comparing ADCs (e.g., B7-H3–, TROP-2–, and SEZ6-targeted agents) with the current SOC as second-line setting are underway/needed to confirm clinical benefit.
- Predictive biomarkers remain undefined; expression of DLL3, B7-H3, and SEZ6 varies across SCLC molecular subtypes.
- Tarlatamab is the SOC for relapsed ES-SCLC; rational sequencing is critical because prior tarlatamab exposure may alter DLL3 expression and/or SCLC molecular subtypes, potentially affecting the activity of subsequent ADCs.

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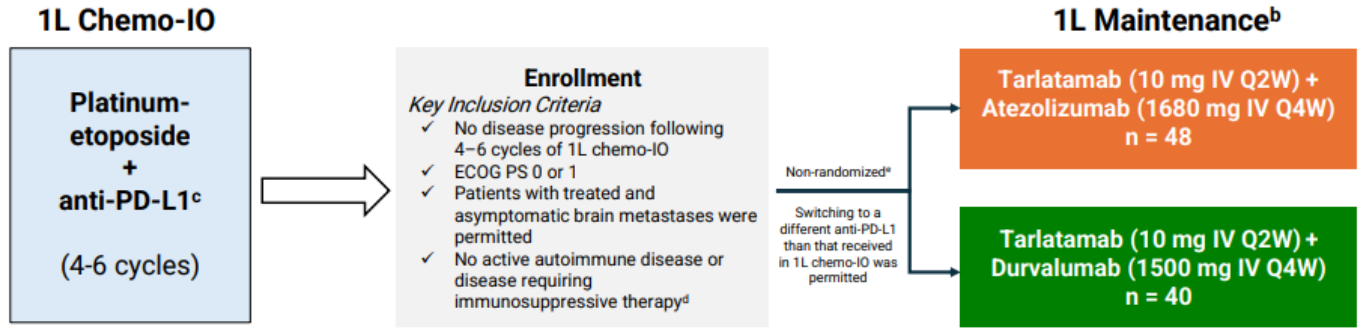
Cáncer de pulmón microcítico - 1ª línea ES

Safety and Survival Update of Tarlatamab with Anti-PD-L1 as First-line Maintenance After Chemo-Immunotherapy for Extensive-Stage Small Cell Lung Cancer: DeLLphi-303 Ph1b Trial

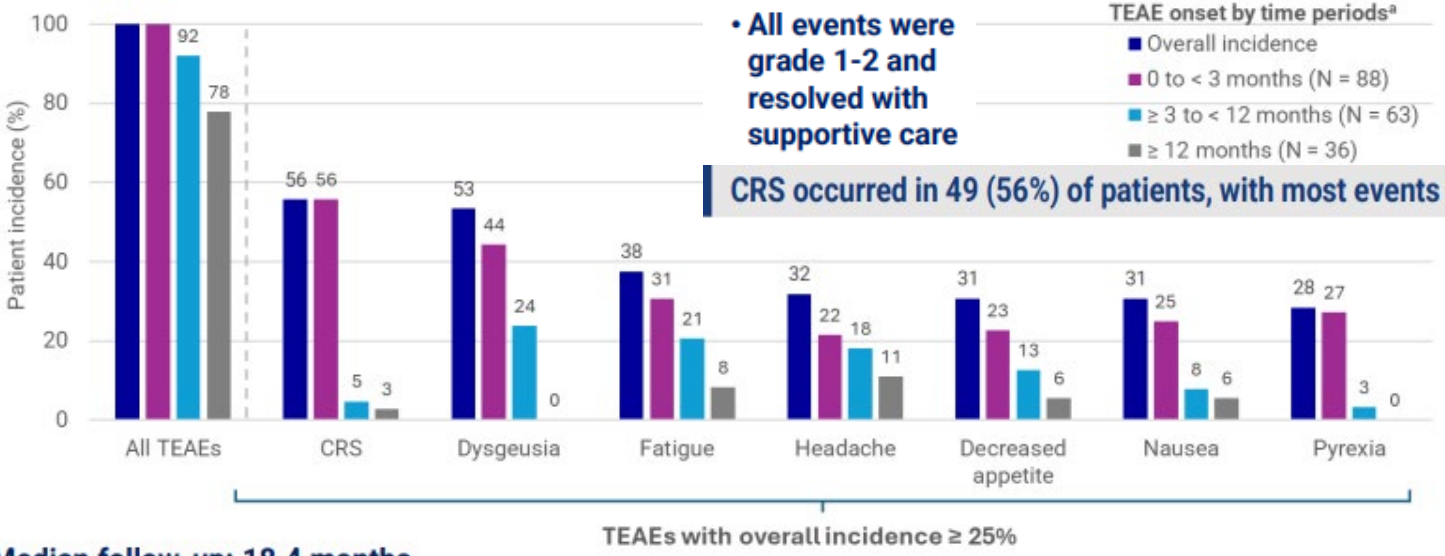
- Current clinical practice guidelines recommend continuation of maintenance anti-PD-L1 (atezolizumab or durvalumab) following first-line (1L) chemo-immunotherapy (chemo-IO) until disease progression or intolerable toxicity.[1, 2]
- Beginning from 1L maintenance, overall survival with anti-PD-L1 monotherapy or anti-PD-L1 combined with lurbinectedin ranges from 10.6-13.2 months.[3,4]
- In our first report of the Phase 1b DeLLphi-303 study (median follow-up: 10.0 months), tarlatamab with anti-PD-L1 as 1L maintenance demonstrated promising survival outcomes (9-month OS of 89%) and a manageable safety profile.[5]

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



Primary Endpoints[f]: Dose-limiting toxicities[g], treatment-emergent and treatment-related adverse events
Secondary Endpoints[h]: Progression-free survival, overall survival, objective response rate, duration of response, and disease control

Here we present extended follow-up (median: 18.4 months) of the DeLLphi-303 study, investigating tarlatamab in combination with anti-PD-L1 as 1L maintenance after chemo-IO for 1L ES-SCLC.



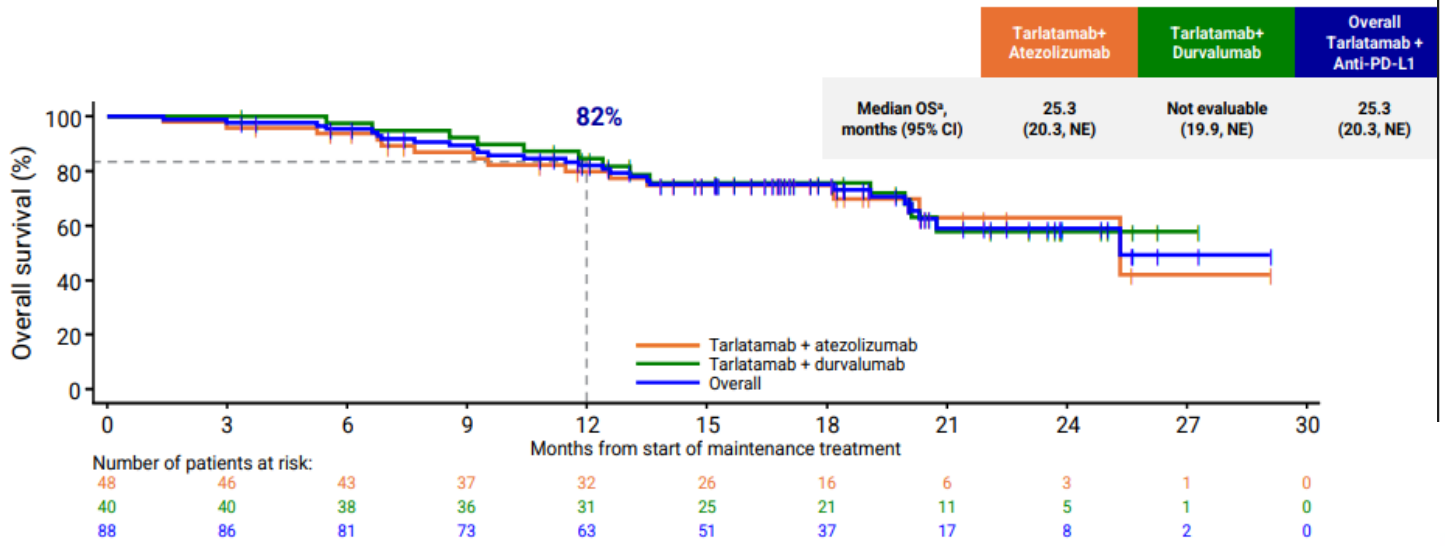
- **All events were grade 1-2 and resolved with supportive care**

TEAE onset by time periods[a]
- Overall incidence
- 0 to < 3 months (N = 88)
- ≥ 3 to < 12 months (N = 63)
- ≥ 12 months (N = 36)

CRS occurred in 49 (56%) of patients, with most events grade 1 (43%) or grade 2 (11%); all CRS events resolved.

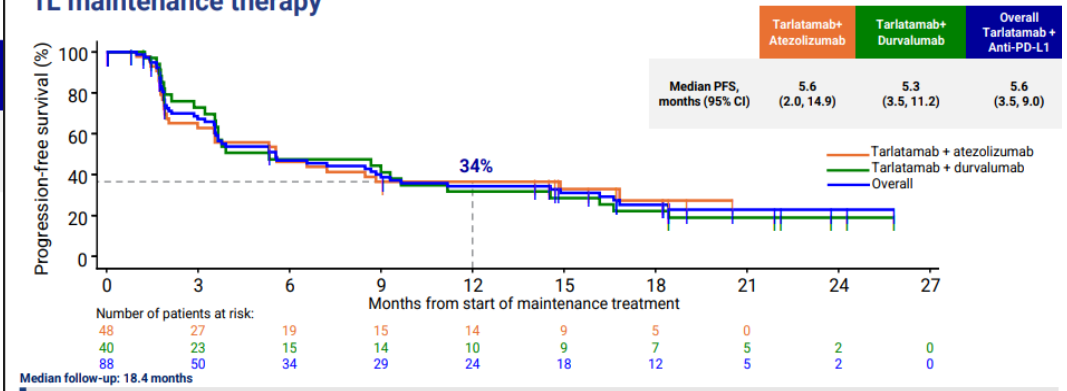
Median follow-up: 18.4 months

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



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

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



Tarlatamab with anti-PD-L1 as 1L maintenance therapy led to a median PFS of 5.6 months (95% CI, 3.5, 9.0).

Summary

Tarlatamab with an anti-PD-L1 as 1L maintenance in ES-SCLC demonstrated:

- **Long-term tolerability with no new safety concerns**
  - No DLTs, no treatment-related fatalities, and low incidence of discontinuations (6%) due to tarlatamab-related AEs
  - TEAEs decreased over time
  - CRS and ICANS events were almost exclusively low grade (grade 1-2)
- **Noteworthy clinical outcomes**
  - From the start of the maintenance period, the median OS for tarlatamab + anti-PD-L1 was 25.3 months, promising compared to standard of care and other emerging therapies
  - The ORR was 24% from a baseline obtained after completion of 1L chemo-IO and median DoR was 16.6 months
  - The overall disease control rate was 60% and the median duration of disease control was 14.6 months, with sustained disease control of ≥ 52 weeks in 36% of patients

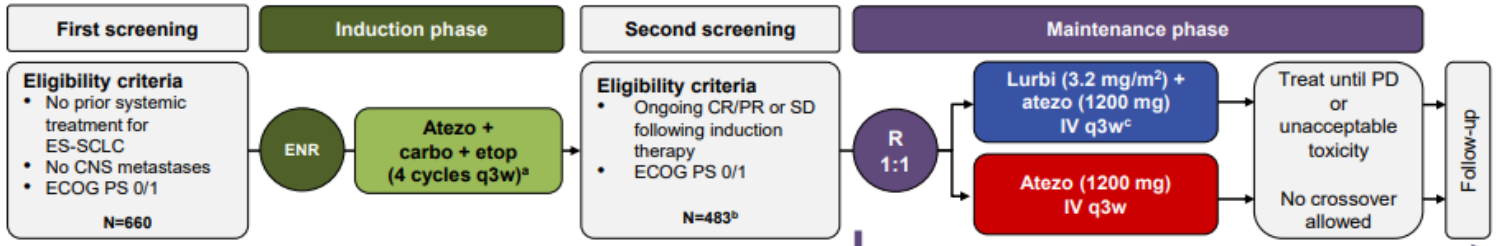
Addition of tarlatamab to anti-PD-L1 as 1L maintenance therapy for ES-SCLC demonstrates a manageable safety profile, sustained disease control, and unprecedented overall survival.

1L: first-line; **AE:** adverse event; **chemo-IO:** chemo-immunotherapy; **CRS:** cytokine release syndrome; **DLT:** dose-limiting toxicity; **DoR:** duration of response; **ES-SCLC:** extensive-stage small cell lung cancer; **ICANS:** immune effector cell-associated neurotoxicity syndrome; **ORR:** objective response rate; **OS:** overall survival; **PD-L1:** programmed death-ligand 1; **TEAE**: treatment-emergent adverse event.

Safety of lurbinectedin + atezolizumab as 1L maintenance treatment in ES-SCLC: results from the Phase 3 IMforte study

Background and study design

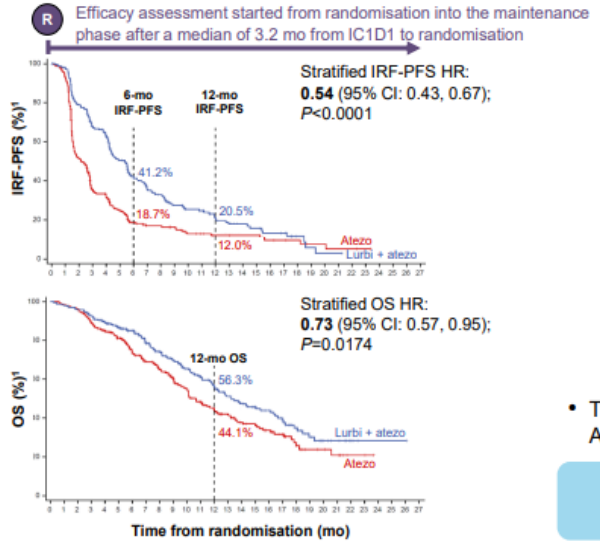
- IMforte is the first Phase 3 study to demonstrate statistically significant and clinically meaningful improvements in PFS and OS with lurbi + atezo vs atezo for 1L maintenance treatment of ES-SCLC



Primary endpoints: IRF-PFS and OS
Secondary endpoints: INV-PFS, ORR, DOR, and safety

MA11.04

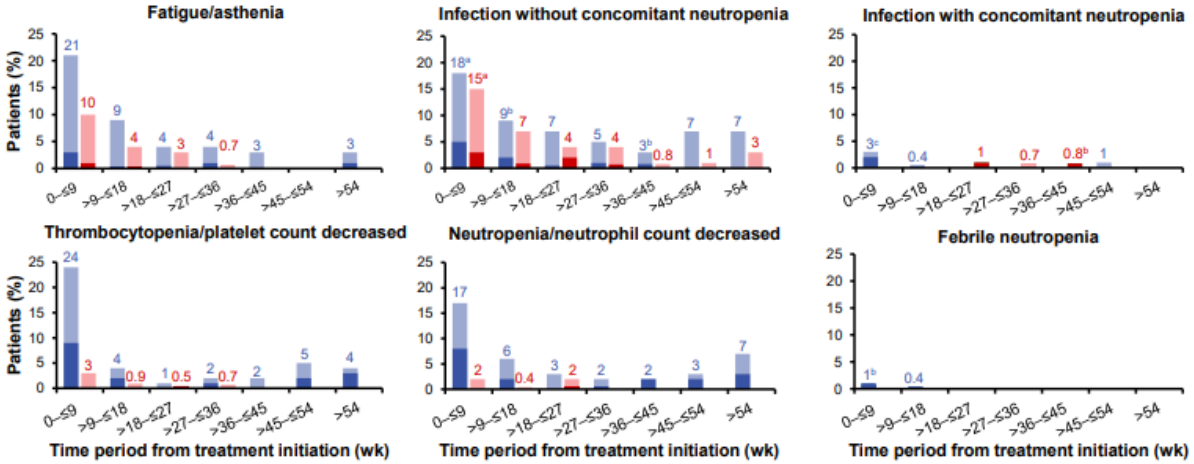
Efficacy and safety summary during the maintenance phase

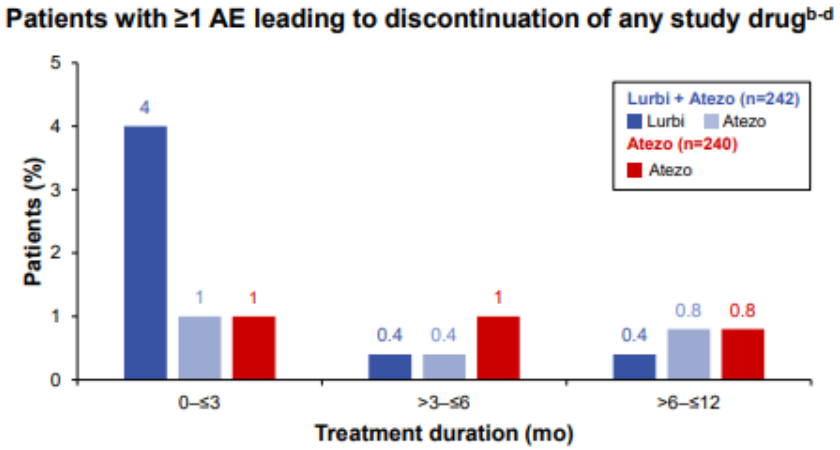


Patients with ≥1 AE, n (%)[1]	Lurbi + atezo (n=242)	Atezo (n=240)
Median treatment duration, mo	4.1 (lurbi)/ 4.2 (atezo)	2.1
All-cause AEs	235 (97.1)	194 (80.8)
Grade 3/4 AEs	92 (38.0)	53 (22.1)
Grade 5 AEs	12 (5.0)	6 (2.5)
Serious AEs	75 (31.0)	41 (17.1)
AEs leading to discontinuation of any study drug	15 (6.2)	8 (3.3)
AEs leading to dose interruption/modification of any study drug[a]	92 (38.0)	33 (13.8)
Lurbinectedin AESIs[b,c]	93 (38.4)	62 (25.8)
Atezolizumab AESIs[b,d]	76 (31.4)	54 (22.5)
Atezolizumab AESI requiring corticosteroids	40 (16.5)	18 (7.5)

- The safety profile of lurbi + atezo was predictable with an increased incidence of AEs, which were mostly low grade; rates of treatment discontinuation were low[1]

We present additional safety data further characterising the tolerability of the combination





Conclusions

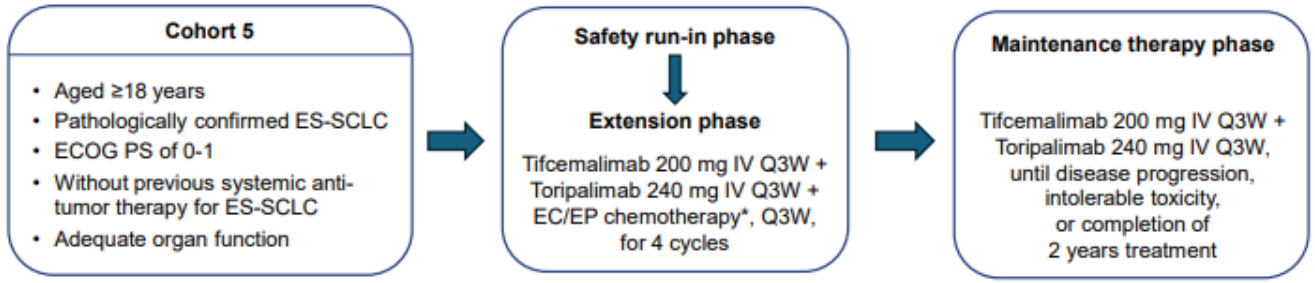
- Although a higher incidence of AEs was noted in the lurbi + atezo arm than in the atezo arm, the majority of AEs were Grade 1/2 and occurred within the first 9 weeks of maintenance treatment
- Lurbi dose reductions and discontinuations occurred mainly in the first 3 months of maintenance treatment
- More atezo dose interruptions were noted in the lurbi + atezo arm; however, the number of patients who discontinued atezo was similar between arms
- Dose interruptions were driven by haematological toxicities
- Rates of AEs leading to any treatment discontinuation were relatively low in both arms
- The majority of Grade 5 AEs in both arms occurred within the first 6 months of maintenance treatment, mostly caused by infectious disorders and considered not related to treatment

Additional safety analyses did not show any unexpected findings or evidence of cumulative toxicity and support a favourable benefit–risk profile of lurbi + atezo, highlighting the combination's potential as a new standard of care for 1L maintenance treatment of ES-SCLC

Tifcemalimab Plus Toripalimab and Chemotherapy as a First-Line Therapy in ES-SCLC: A Phase Ib/II Study

- BTLA is PD-1 like molecule and co-expressed on the surface of activated B and T cells with PD-1, BTLA blockade promotes tumor specific T cell response and works synergistically with PD-1 blockade.
- Tifcemalimab (JS004 or TAB004), a humanized IgG4 monoclonal antibody that binds BTLA and blocks its interaction with its ligand Herpes virus Entry Mediator (HVEM).
- Previous phase I/II study revealed preliminary anti-tumor activities of Tifcemalimab plus toripalimab (anti-PD-1) in the later setting of ES-SCLC.
- A multi-cohort phase Ib/II study (NCT05664971) was conducted to evaluate the safety and efficacy of tifcemalimab plus toripalimab and chemotherapy in the 1st setting for patients with advanced lung cancer.

A multi-cohort phase Ib/II study (NCT05664971)



* Etoposide d1-3, 100 mg/m² + carboplatin d1, AUC=5 or cisplatin d1, 75 mg/m²

- **Primary endpoints:** Safety per NCI-CTCAE v5.0 and ORR by investigator per RECIST v1.1
- **Secondary endpoints:** DCR, DoR, PFS, and OS

Conclusion

- **Tifcemalimab in combination with toripalimab and chemotherapy demonstrated promising antitumor activity as a 1st line treatment for patients with ES-SCLC.**
  - ORR: 86%
  - Median PFS: 5.7 m
  - Median OS: 17.9 m
- **The combination showed a predictable and manageable safety profile; no new safety signals or toxicities were identified.**
- **The results from this phase I/II study support tifcemalimab plus toripalimab and chemotherapy as a potential treatment option for patients with ES-SCLC and further investigation is warranted.**

MA11.03

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lung cancer research

Mesotelioma

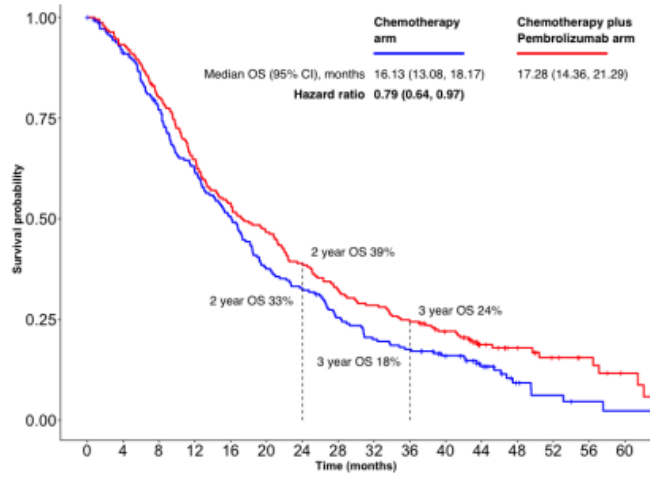
IASLC Mesothelioma Staging Project: Impact of Molecular Alterations on Survival in a Cohort From 9th Edition Database

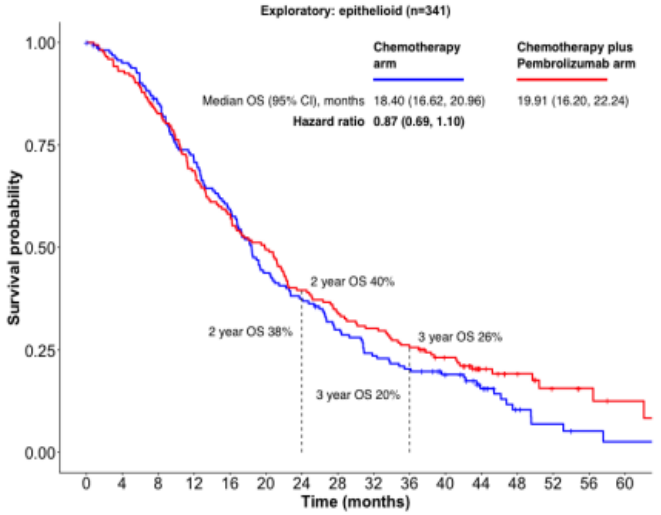
- While tumor histology and the current Tumor, Node, Metastasis (TNM) staging system have been used for prognostication of pleural mesothelioma (PM), outcomes still vary among histologic subtypes and staging groups, highlighting the need for further risk stratification to guide clinical management
- Several studies have shown the prognostic significance of genomic biomarkers including BAP1, NF2, CDKN2A, and others
- However, the extent to which these biomarkers contribute to survival prediction beyond established clinical prognostic factors remains unclear
- To explore this, we examined the impact of molecular alterations on overall survival (OS) from a real-world, multi-institutional pilot cohort included in the IASLC 9th edition Staging Project to help guide data collection for the planned 10th edition of the PM staging system

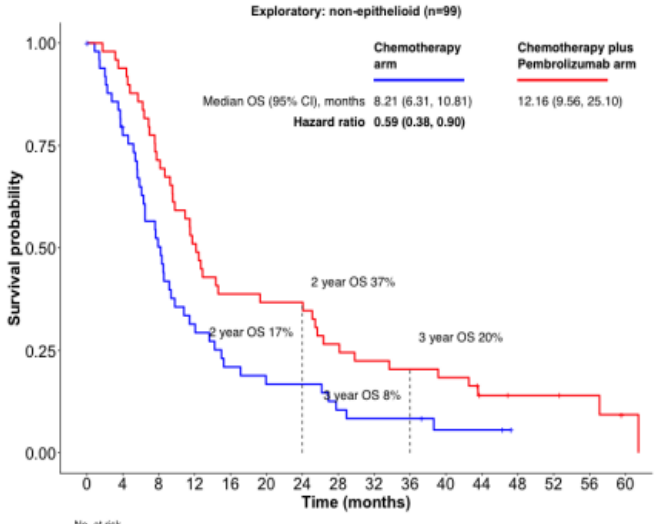
- A three-institutional database from the 9th edition: PM diagnosed from 2013-2022
- Focused on a targeted panel of biomarkers assessed using local assays
  - Somatic genes (NGS): BAP1, CDKN2A, NF2, SETD2, TP53
  - IHC-based: BAP1, PD-L1 (% tumor cells)
- Genomic alterations classified as pathogenic, variants of unknown significance (VUS), and wild type; VUS excluded
- Hazard ratios for molecular factors adjusted for clinical covariate data: age, sex, histologic subtype, performance status, curative-intention resection, T/M group

Conclusions

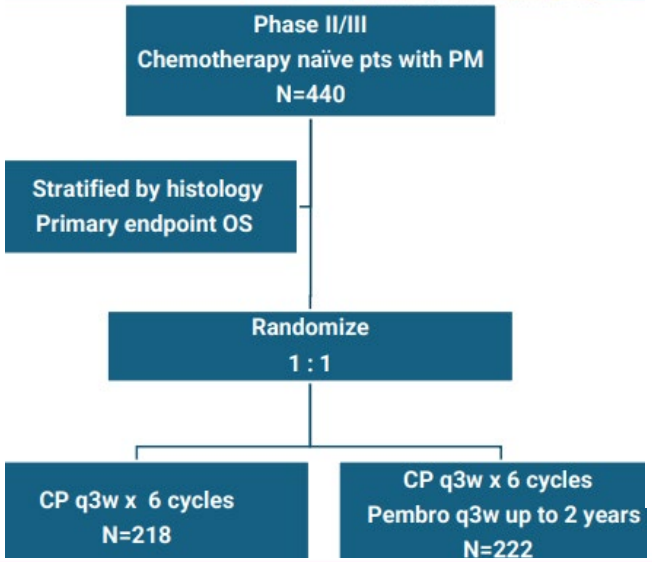
- In this large, multi-institutional real-world cohort of PM, pathogenic alterations in BAP1, NF2, CDKN2A, TP53, SETD2 were analyzed using NGS and expression of BAP1 and PD-L1 were evaluated using IHC
- Focusing on histologic subtypes, pathogenic alterations in CDKN2A and NF2 were enriched in non-epithelioid PM, whereas BAP1 loss by IHC was associated with epithelioid PM
- Integrated analysis of BAP1 using NGS and IHC suggests concordance and the potential utility of co-testing
- Pathogenic alterations in CDKN2A, NF2 and TP53 were associated with worse OS, while pathogenic alterations in BAP1 and loss of expression of BAP1 by IHC were associated with better OS, independent of histologic subtype and clinical variables
- Modeling suggests that a panel of genomic alterations could provide additional prognostic information beyond traditional clinical factors including anatomic TNM and histologic subtype
- Our findings corroborate but also augment previously published association of genomic alterations in PM
- Future studies are needed to determine whether genomic alterations should be formally added to the anatomic TNM stage classification of PM to create prognostic stage groups







Exploratory Analyses of Canadian Cancer Trials Group trial IND227: a randomized trial of chemotherapy with and without pembrolizumab in advanced pleural mesothelioma (PM)



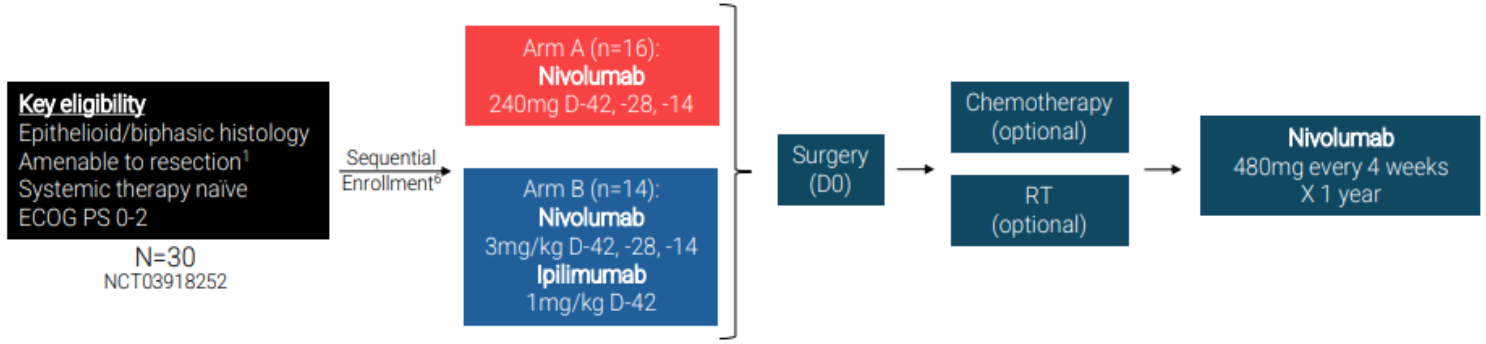
Conclusions

- The improvement in survival with the addition of pembrolizumab to standard platinum-pemetrexed chemotherapy in advanced pleural mesothelioma is maintained with additional follow-up
- Interestingly, the median and 2- and 3-year overall survival observed with pembrolizumab alone was reasonable and could warrant additional study
- BAP1 loss was associated with a better outcome in all patients, while loss of MTAP was negatively prognostic; neither was predictive
  - Consideration may need to be given to stratifying for these variables in future studies

OA12.02

Neoadjuvant nivolumab or nivolumab plus ipilimumab in resectable diffuse pleural mesothelioma

- The role of surgery in diffuse pleural mesothelioma (DPM) is controversial.
- Retrospective and single-arm trials suggest signal of benefit for aggressive tri-modality therapy (chemotherapy, surgery, radiation) in DPM.
- Large randomized trials in DPM have failed to show a survival benefit for surgery in pre-immunotherapy era.
- Peri-operative immunotherapy-containing regimens have been transformative in several malignancies, and are a frontline standard for unresectable DPM.

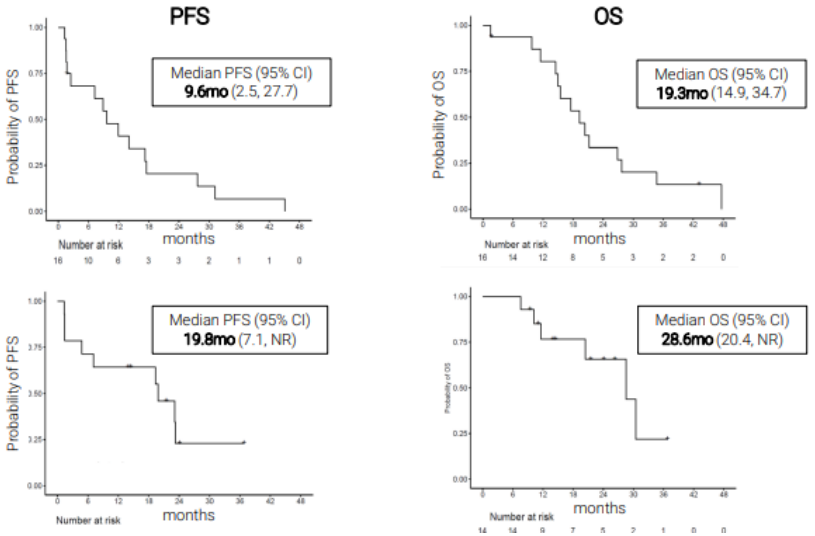


Primary Endpoints: Feasibility, Safety
Secondary Endpoints: ORR[2], Safety of adjuvant nivo[3]
Exploratory Endpoints: PFS[4], OS[5], Longitudinal ctDNA assessment, genomic/immunologic analyses, gut microbiome

- In this phase 2 multi-arm trial (NCT30918252), we explored the feasibility and safety of neoadjuvant nivolumab (nivo) and nivolumab/ipilimumab (nivo/ipi) in potentially resectable DPM, including an evaluation of the clinical utility of tumor-informed ctDNA minimal residual disease assessment.

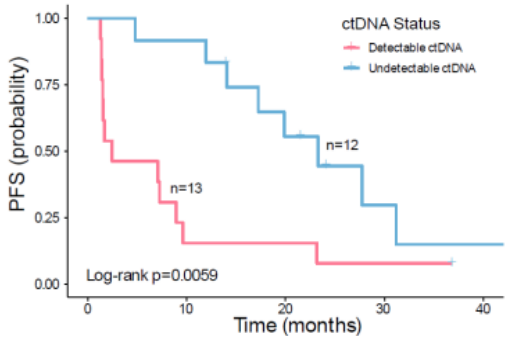
Nivo
n=16
Median f/u 43.2mo

Nivo plus Ipi
n=14
Median f/u 24.1mo

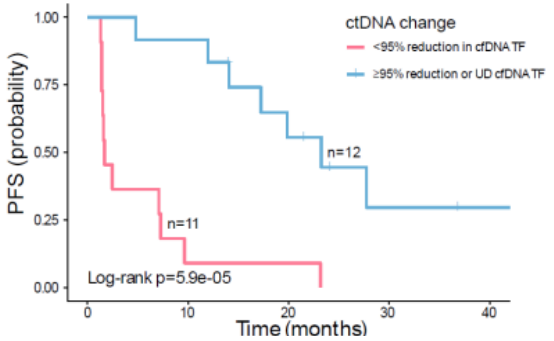


Association between pre-surgery ctDNA status and PFS

ctDNA residual disease (pre-surgery)



ctDNA dynamics (pre-surgery)



Concluding remarks

- Neoadjuvant nivo and nivo/ipi demonstrated an acceptable safety profile that did not inhibit surgical resection.
- Neoadjuvant nivo and nivo/ipi were feasible, without delay of planned surgery.
- Neoadjuvant nivo/ipi demonstrated a potential signal of clinical benefit compared to historical data with systemic therapy alone.
- Ultra-sensitive tumor-informed WGS single and serial ctDNA assessments successfully captured clinical endpoints.
- All patients who experienced disease progression precluding surgery had detectable ctDNA prior to resection.
- Undetectable or >95% ctDNA reduction prior to surgery appeared to be associated with improved PFS.

- **Future studies are needed to prospectively (1) determine the clinical utility of peri-operative immunotherapy in potentially resectable DPM and (2) solidify the timing, definition and clinical sensitivity of ctDNA as an efficacy assessment tool in DPM.**

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Muchas gracias