Microcitoma Polmonare: quali novità?

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ISTITUTI DI RICOVERO E CURA A CARATTERE SCIENTIFICO

Disclosures

- Dr Minuti discloses the following conflicts of interest:
- Fees for membership of an advisory board or lectures or medical writer from:

A. Astra-Zeneca
B. Roche
C. BMS
D. Gilead
E. Novartis
F. Sanofi
G. Amgen
H. MSD
I. Johnson & Johnson
J. Daiichi Sankyo

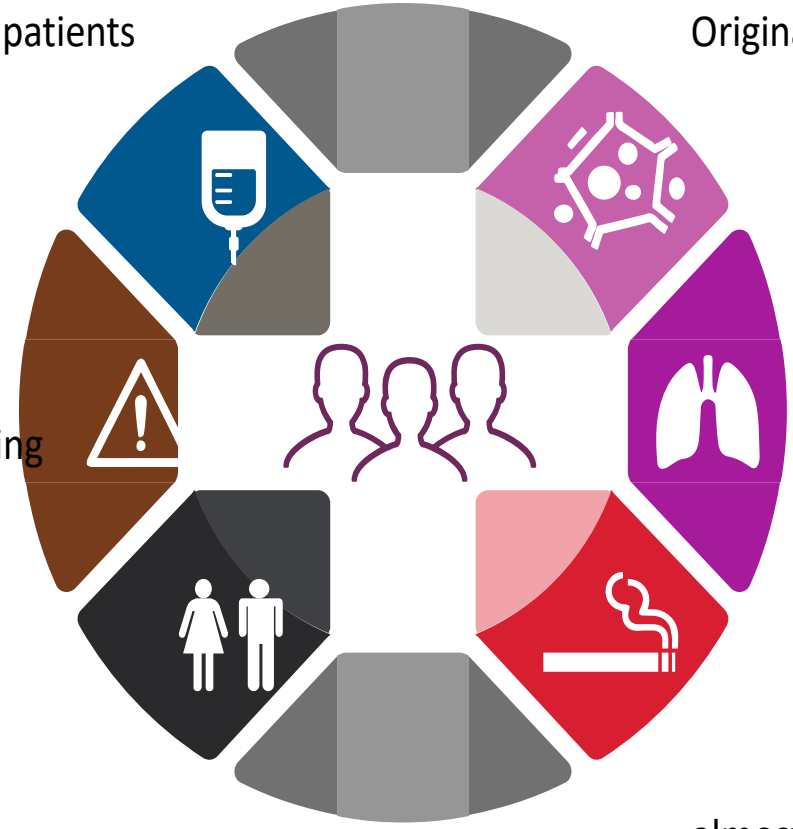
Small-Cell LC remains the biggest challenge in thoracic oncology

Poor prognosis

Highly sensitive to initial chemo, but most patients relapse and die within 2 years

Neuroendocrine tumor

Originating from neuroendocrine cells



Aggressive

Fast-growing tumor characterized by high mitotic rate and early metastasis, requiring rapid intervention

Comorbidities

Frequently exhibit COPD, ischemic cardiomyopathy and hypertension

Clinical presentation

Typically with short anamnesis, symptoms of dyspnea and persistent cough

Smoking

SCLC occurs almost exclusively in smokers

Rekhtman. Arch Pathol Lab Mad 2010; Carter, et al. RadioGraphics 2014; Pusceddu, et al. Crit Rev Oncol Hematol 2016; Sabari, et al. Nat Rev Clin Oncol 2017

SCLC management in clinical practice

1. **Decipher disease**
   - ✓ Accurate staging – TNM System, 8 th version preferred*
   - ✓ Accurate patient evaluation (age, PS, comorbidities, cancer-related symptoms, …….)

2. **Define the goal of treatment**
   - ✓ Curative
   - ✓ Palliative (even in LD-SCLC)

3. **Consider facilities**
   - ✓ Access to multidisciplinary team, including RT units
   - ✓ Availability of Palliative team

4. **Start treatment**
   - ✓ Timing

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*Farago AF, Transl Lung Cancer Res 2918; Rami-Porta R, CA Cancer J Clin 2017; Detterbeck FC, Chest 2017

SCLC and Simultaneous Care

Journal Pre-proof

Simultaneous Care provision to patients with Small Cell Lung Cancer in Lazio region: practical recommendations of a multidisciplinary group

Sabrina Mariotti, Gabriele Minuti, Lorenza Landi, Emilio Bria, Giorgia Carlucci, Mariantonietta Di Salvatore, Raffaele Giusti, Aurelia Iurato, Sara Ramella, Maria Adelaide Ricciotti, Gian Paolo Spinelli, Marco Tineri, Francesco Scarcella, Mario Rosario D'andrea

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Mariotti S. et al. (Minuti G. corresponding author) HELIYON 2024 in press

Selected clinical trials with IO in LS-SCLC

Trial	Ph	Setting	Study Arm(s): E) Experimental; C) Control	*N*	Primary End-point (s)	Main Results/Status	Start Date–Estimated completion rate
STIMULI (NCT02046733)	II	Maintenance after CRT	E) nivolumab + ipilimumab C) observation	E) 78 C) 75	PFS, OS	mPFS: 10.7 vs. 14.5 [HR = 1.02 (0.66-1.58), 2-sided p = 0.93]; mOS: NR vs. 32.1 [HR = 0.95 (0.59-1.52), p = 0.82]	July 28, 2014–January 2022 (completed early in 2019)
ADRIATIC (NCT03703297)	III	Maintenance after CRT	E) durvalumab +/- tremelimumab C) placebo	724	PFS, OS	Ongoing	September 27, 2018–May 10, 2024
LU-005 (NCT03811002)	II/III	Concurrent with CRT	E) CRT + atezolizumab C) CRT	506	PFS, OS	Ongoing	May 28, 2019–December 28, 2026
ACHILES (NCT03540420)	II	Maintenance after CRT	E) atezolizumab C) observation	212	2-year survival	Ongoing	July 31 2018–December 2026
NCT04189094	II	Induction and maintenance after CRT	E) sintilimab + PE → CRT → sintilimab C) PE → CRT	140	PFS	Ongoing	January 1, 2020–July 1, 2023
NCT04308785	II	Maintenance after CRT	E) atezolizumab + tiragolumab C) atezolizumab + placebo	150	PFS	Ongoing	December 1, 2021–February 15, 2025
NCT04952597	II	Concurrent and maintenance after CRT	E) CRT + ociperlimab + tislelizumab → ociperlimab + tislelizumab E) CRT + tislelizumab → tislelizumab C) CRT	120	PFS	Ongoing	July 15, 2021–March 30, 2024

PE, platinum-etoposide; CRT, concomitant chemoradiotherapy.

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Belluomini L, et al. Fontiers Oncol 2022

Phase III, ADRIATIC trial, LS-SCLC

Ongoing, randomised, double-blind, placebo-controlled, multicentre, international study

- Stage I–III LS-SCLC (stage I/II inoperable)
- WHO PS 0 or 1
- Had not progressed following cCRT*
- PCI* permitted before randomisation

N=730

R†

Stratified by:
Disease stage (I/II vs III)
PCI (yes vs no)

- **Durvalumab** N=264
- **Placebo** N=266
- **Durvalumab + tremelimumab** N=200

Treatment until investigator-determined PD or intolerable toxicity, or for a **maximum of 24 months**

Dual primary endpoints:
- D vs P
  - PFS,‡ OS

Key secondary endpoints:
- D+T vs P
  - PFS,‡ OS

Other secondary endpoints:
- PFS/OS landmarks, safety

At the first interim analysis:[1]
- Consolidation durvalumab significantly improved the dual primary endpoints of OS and PFS versus placebo; generally consistent treatment benefit across predefined patient subgroups
- Treatment well tolerated; safety consistent with known safety profile of durvalumab in the post-cCRT setting
- Durvalumab + tremelimumab arm remained blinded

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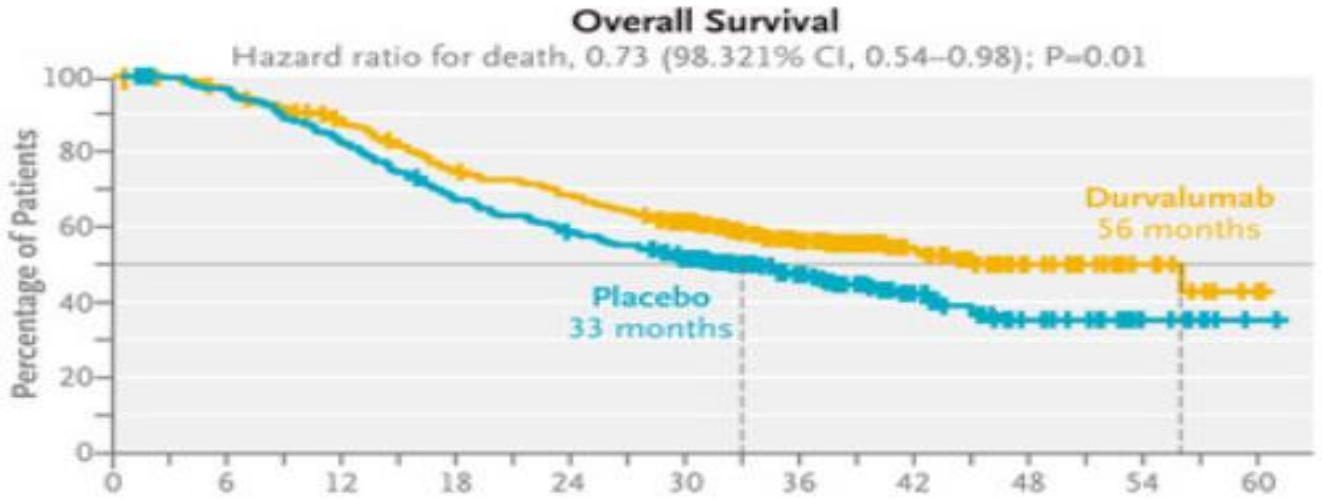
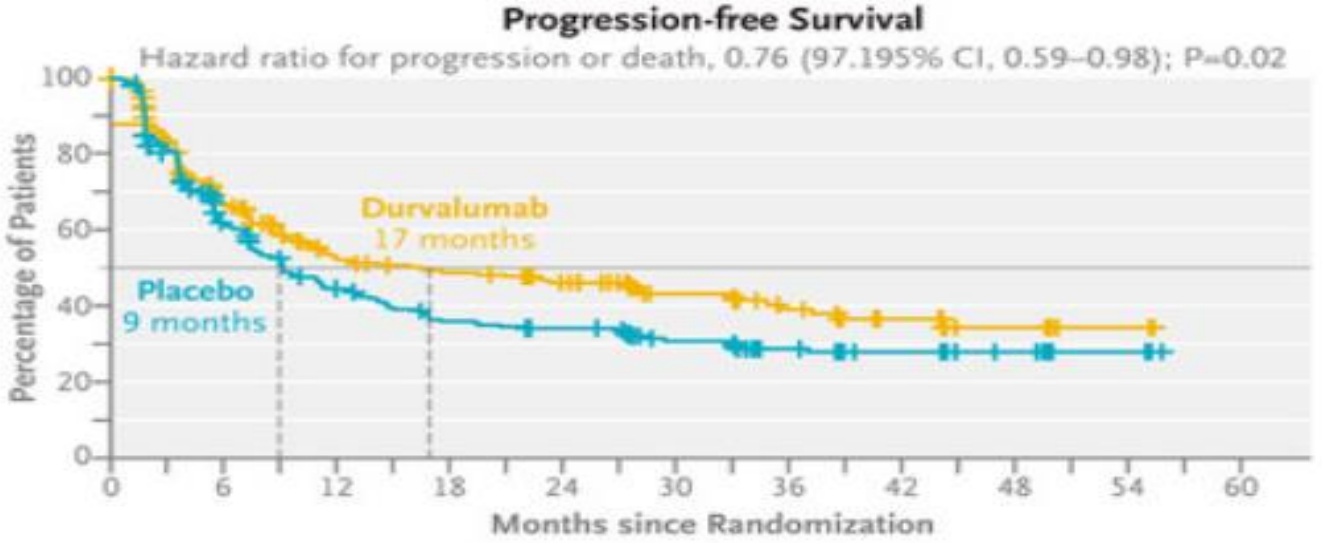
Cheng J et al. NEJM 2024

Phase III, ADRIATIC trial, LS-SCLC, Dual primary end-point

OS
HR 0.73
56 vs 33 m.

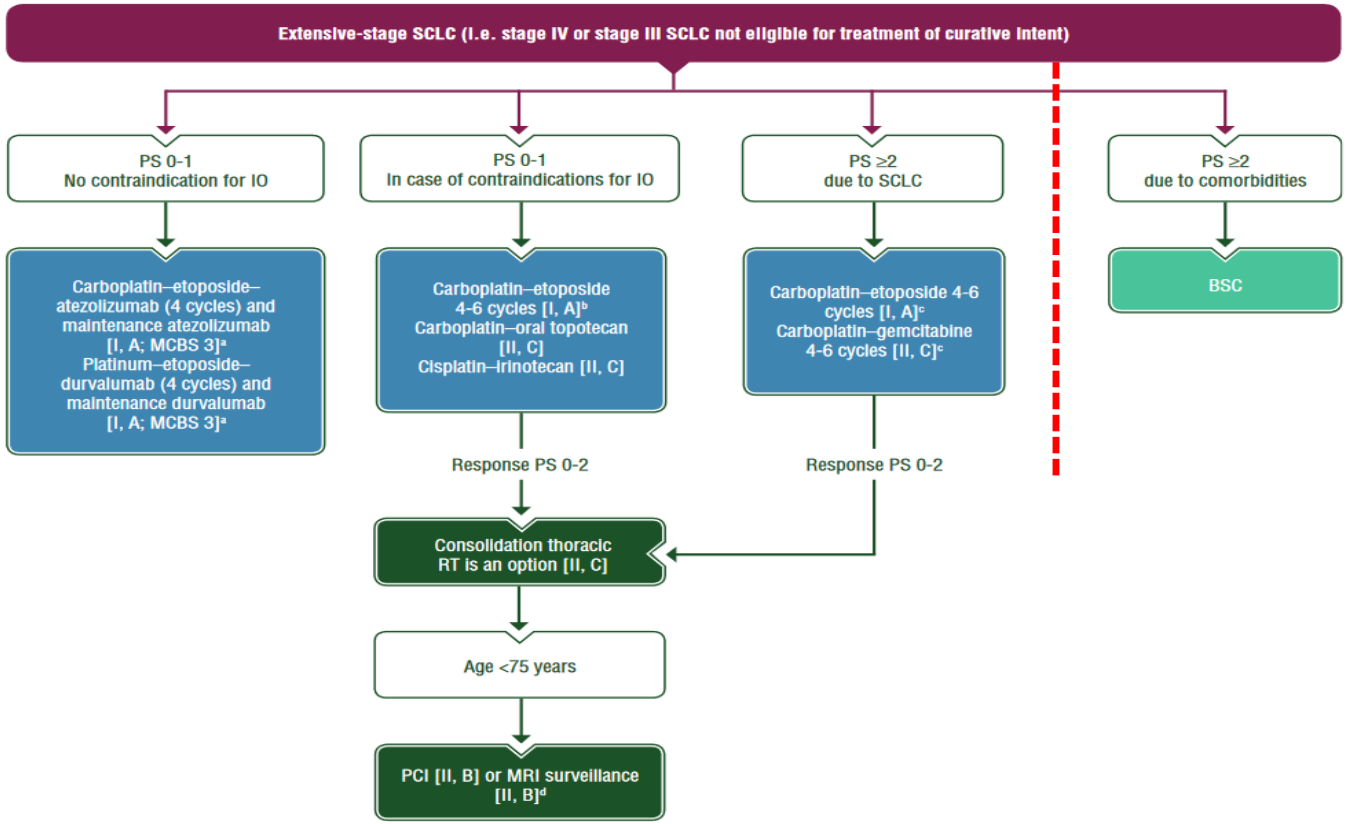


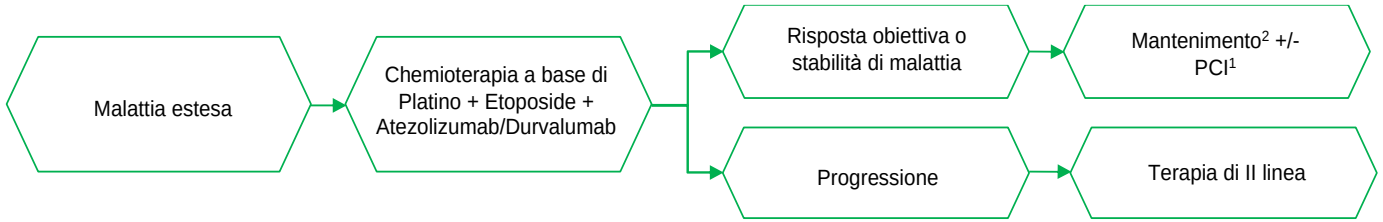
PFS
HR 0.73
17 vs 9 m.



Cheng J et al. NEJM 2024

ED-SCLC: ESMO, AIOM Guidelines & Evidence





- **CT-IO concomitante è SoC** (non ritardare avvio IO)
- **PS 2** da malattia vs co-morbilità?

- **Consolidamento TRT post-IO** (30 Gy/10 fr): valutare in pazienti PS 0-1, in risposta, con residuo (basso carico sistemico di malattia)

ASTRO

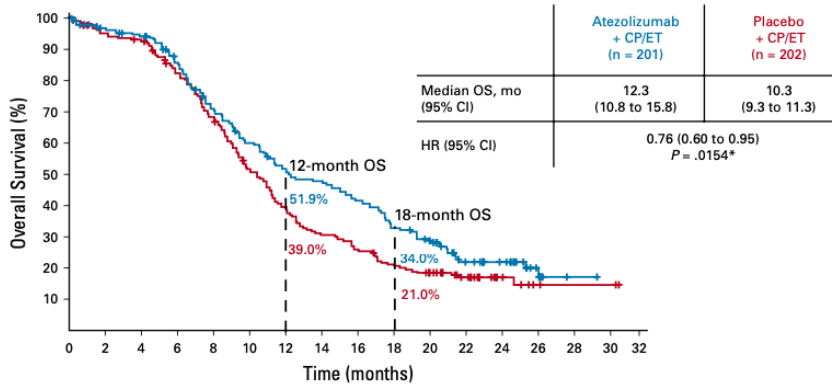
- **PCI** (con risparmio ippocampo) o **sorveglianza con RM** (se adeguato staging SNC)

1. PCI raccomandata in caso di risposta obiettiva alla chemioterapia di I linea
2. Mantenimento con Atezolizumab/Durvalumab

Dingemans AM et al, Ann Oncol 2021 (LG ESMO); LG AIOM; Agarwal M et al, Cancer 2023; Kurshid H et al, JCO 2023; Slotman BJ et al, Lancet 2015; LG ASTRO Pract Radiat Oncol 2020; Sun A et al, Lung Cancer 2023; Slotman BJ et al, NEJM 2007; Takahashi T et al, Lancet Oncol 2017

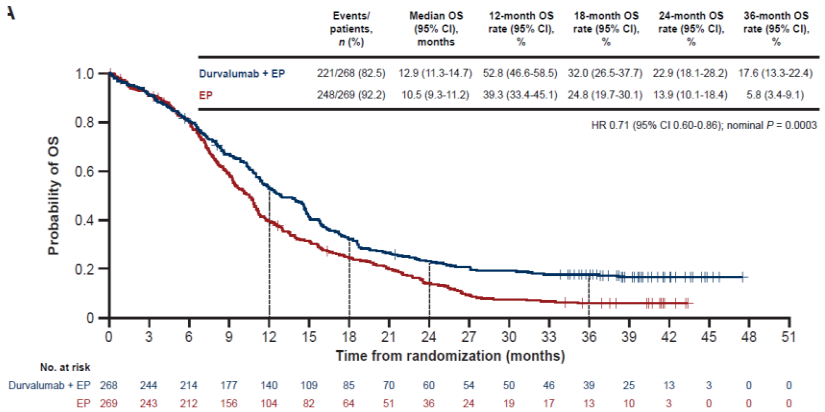
CT/IO in ES-SCLC: Consistent results across 5 trials

IMPOWER 133
Atezolizumab– Anti PD-L1



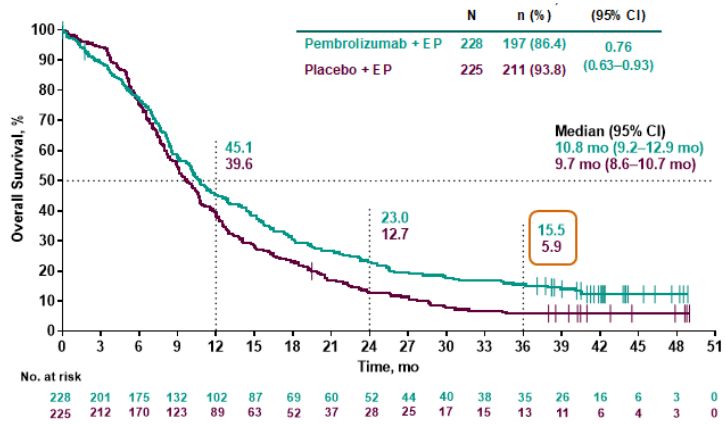
Liu S, et al. JCO 2021

CASPIAN
Durvalumab – Anti PD-L1



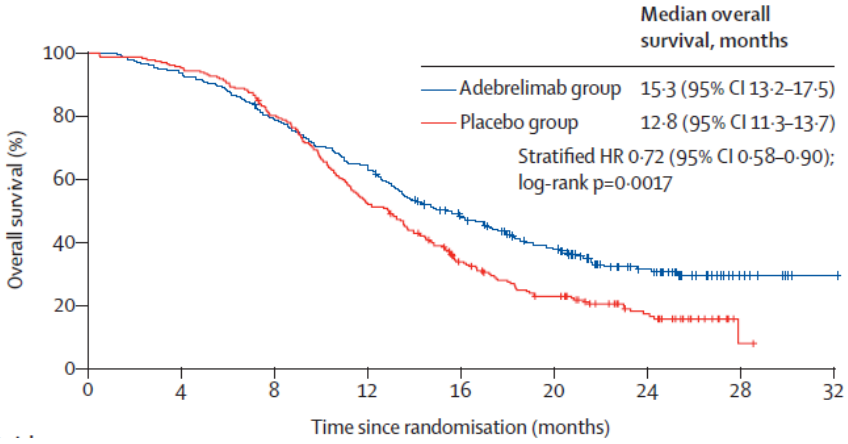
Paz-Ares L, et al. ESMO Open 2022

KEYNOTE 604
Pembrolizumab – Anti PD-1



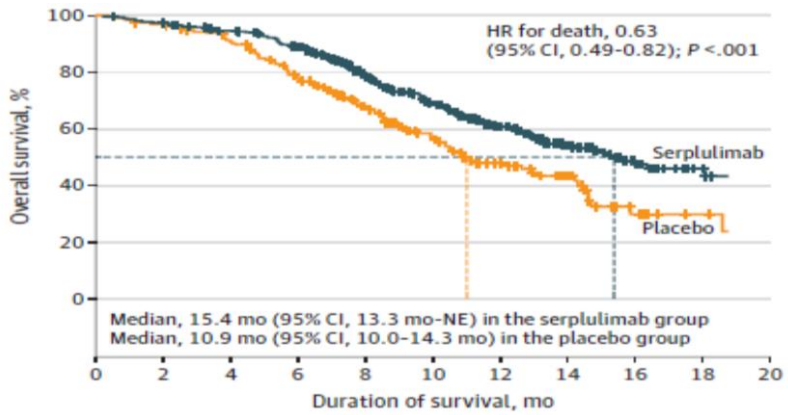
Rudin C, WCLC 2022

CAPSTONE 1
Adrelimab – Anti PD-L1



Wang J, et al. Lancet Oncol 2022

ASTRUM 005
Serplulimab - Anti-PD-1



Cheng Y, JAMA 2022

Pivotal Trials – Long term outcome

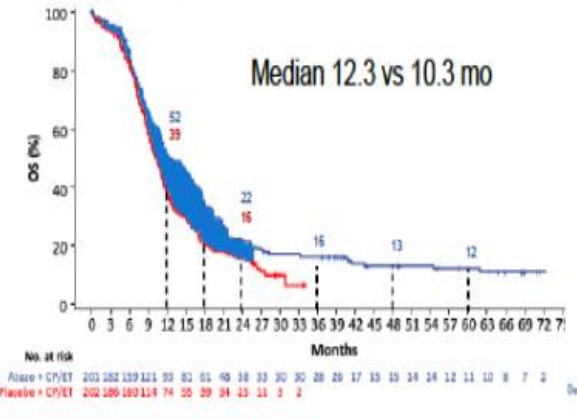
OS Rates, %	A+CE (n=201)	P+CE (n=202)
IMpower133 (CCOD: 24 Sep 2022)		
1 year	52	39
2 years	22	16
IMpower133 and IMbrella A (CCOD: 16 Mar 2023)		
3 years	16	NE[a]
4 years	13	NE[a]
5 years	12	NE[a]

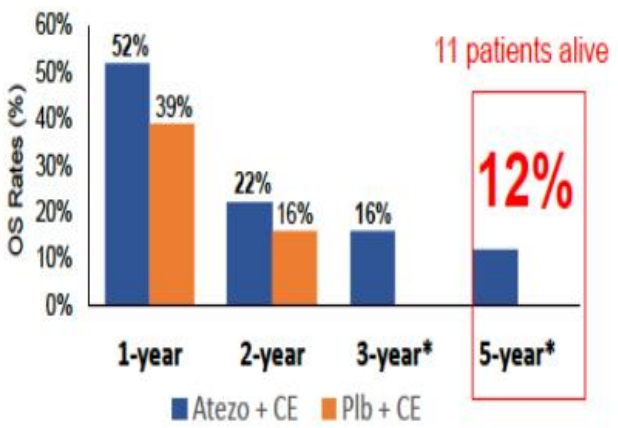
NE, not estimable. [a]OS rates were NE in the P+CE arm (no roll-over to IMbrella

IMbrella:
Phase IV, single arm, ATEZO + CP/ET, extension and long-term observational study (NCT03148418)

IMpower133 and IMbrella A

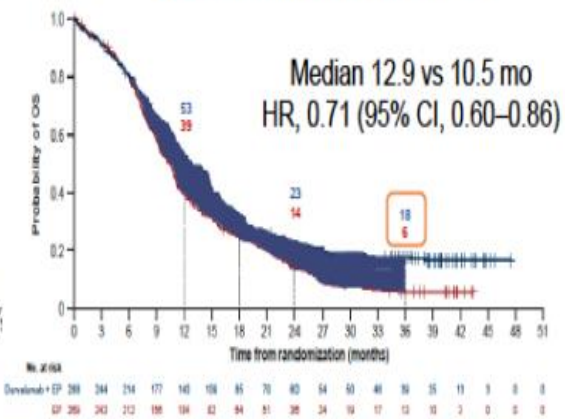
Atezolizumab + CP/ET vs CP/ET + Plb[1-2]

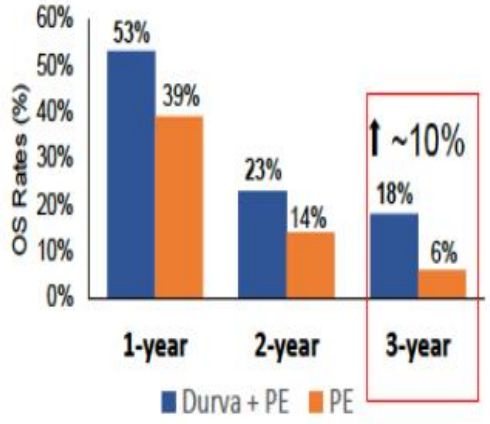




CASPIAN

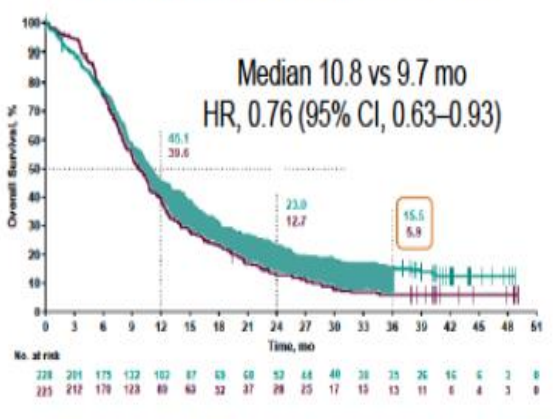
Durvalumab + P/ET vs P/ET[3-4]

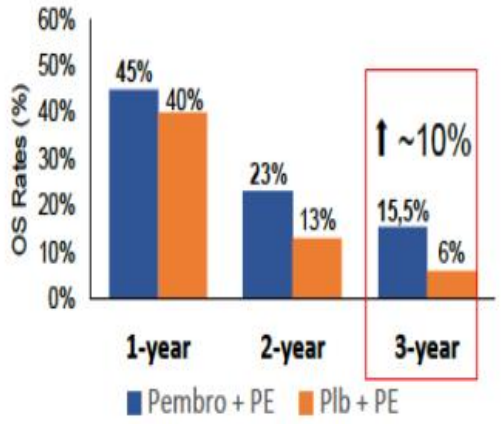




KEYNOTE-604

Pembrolizumab + P/ET vs P/ET + Plb[5-6]





CP, carboplatin; ET, etoposide; P, platinum; Plb, placebo; NE, not estimable. * OS rates at 3-5 years were not estimable in the control arm as rollover to IMbrella A was not permitted.

1.- Horn L, et al. N Engl J Med 2018; 2.- Liu S, et al. OA01.04, WCLC 2023; 3.- Paz-Ares L, et al. Lancet 2019; 4.- Paz-Ares L, et al. ESMO Open 2022; 5.- Rudin CM, et al. J Clin Oncol 2020; 6.- Rudin CM, et al. WCLC 2022

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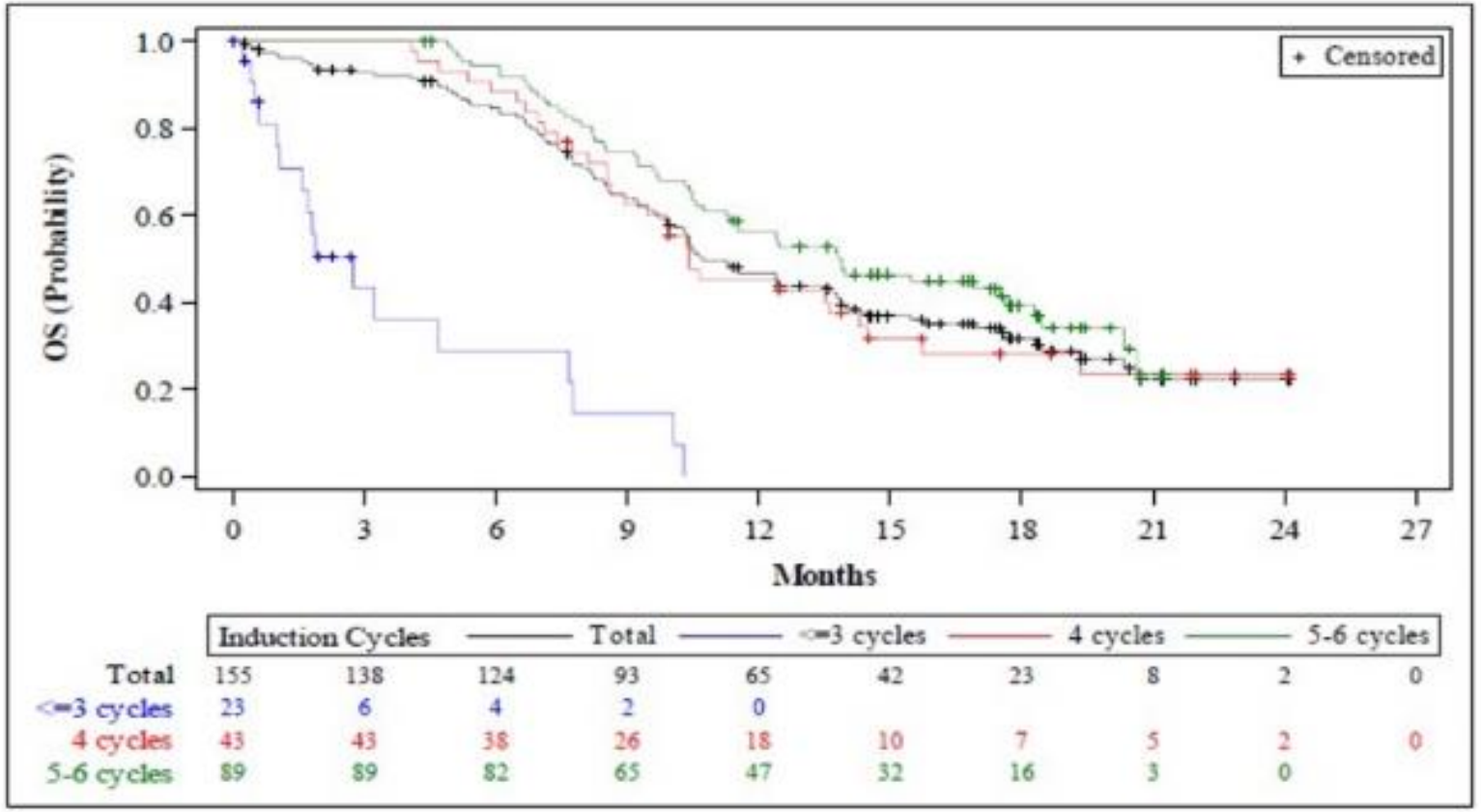
CT-IO for SCLC-ED in real-life population: phase IIIb MAURIS as an exemple

- ✓ **Role of CT/IT in cancer-related ECOG PS2**
- ✓ **Role of prolonged CT (6 versus 4 cycles)**
- ✓ **Role of thoracic RT after response to CT/IT**
- ✓ **Role of PCI in responding patients (irrespective of front-line CT or CT/IT)**



- **Efficacy Results**
- Overall survival (OS)

The median OS in the overall ITT population **was 10.7 months** (95% CI, 9.9 to 13.7 months.) Figure 1 shows the results of OS by subgroup (number of cycles of induction) The median OS was longer in patients who performed **5-6 induction cycles (13.8 months**, 95% CI, 10.7 to 18.2 months) than in those who performed 4 cycles (10.4 months, 95% CI, 8.6 to 14.2 months) or ≤ 3 cycles (2.7 months, 95% CI, 1.0 to 7.6 months.)

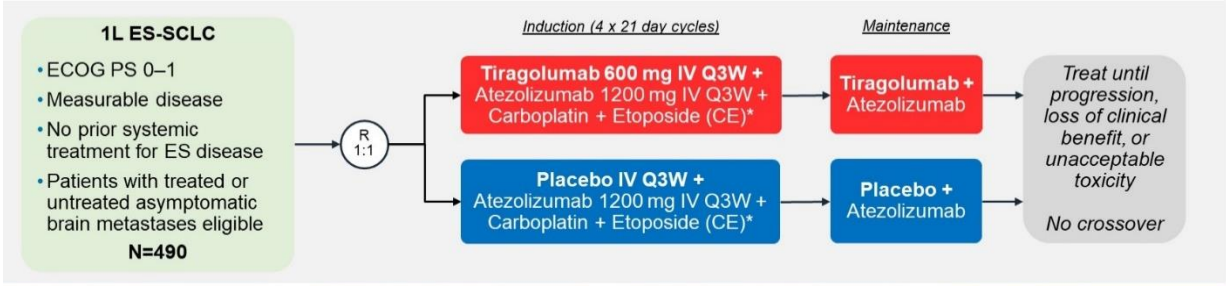
mOS and mPFS were 10.7 and 5.5 months, respectively

Bria E et al. The Oncologist 2024

No benefit by adding anti-TIGIT to standard CT-IO

Role of PVR in SCLC

SKYSCRAPER-02



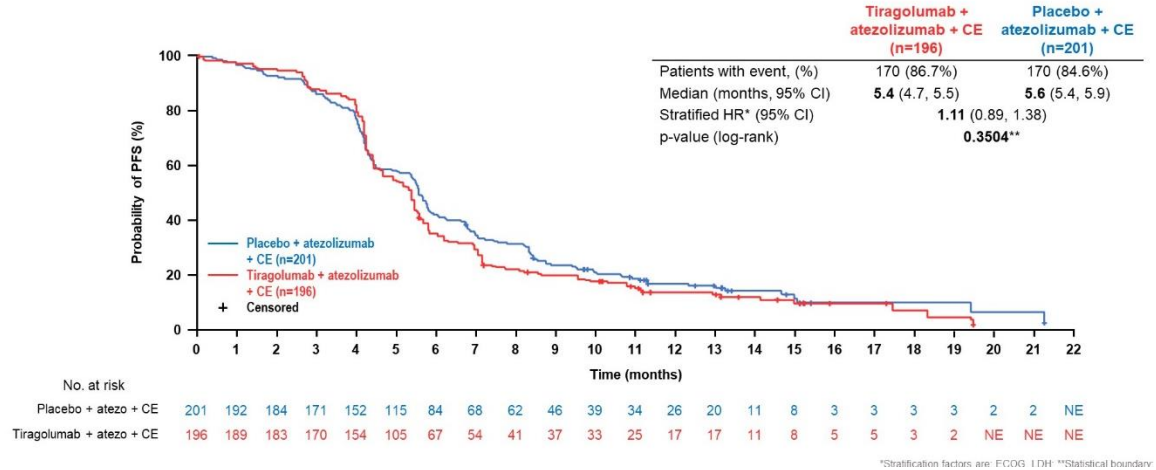
Stratification Factors:
- **ECOG PS** (0 vs. 1)
- **Brain metastases** (Yes vs. No)
- **LDH** (≤ ULN vs. > ULN)

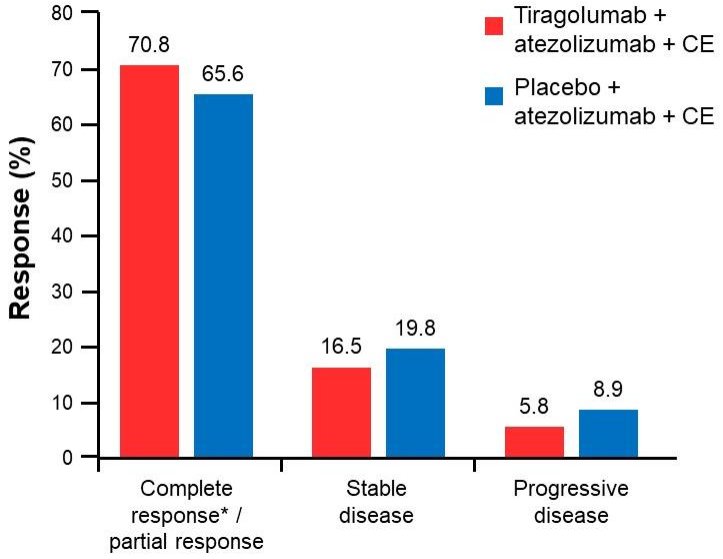
Co-Primary Endpoints:
- OS and investigator-assessed PFS in **Primary Analysis Set** (all randomized patients without presence or history of brain metastases at baseline)

Secondary Endpoints:
- PFS and OS in **Full Analysis Set** (all randomized patients)
- Confirmed objective response rate
- Duration of response
- Safety
- Pharmacokinetics
- PROs

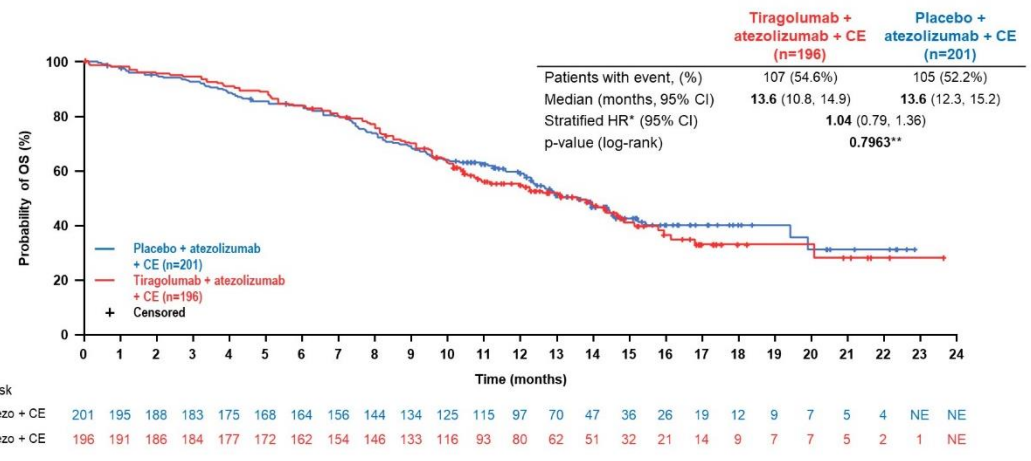
Primary analysis
- Cut-off date of 6 February 2022
- Median follow-up of 14.3 months (Primary Analysis Set)

PFS: Primary Analysis Set



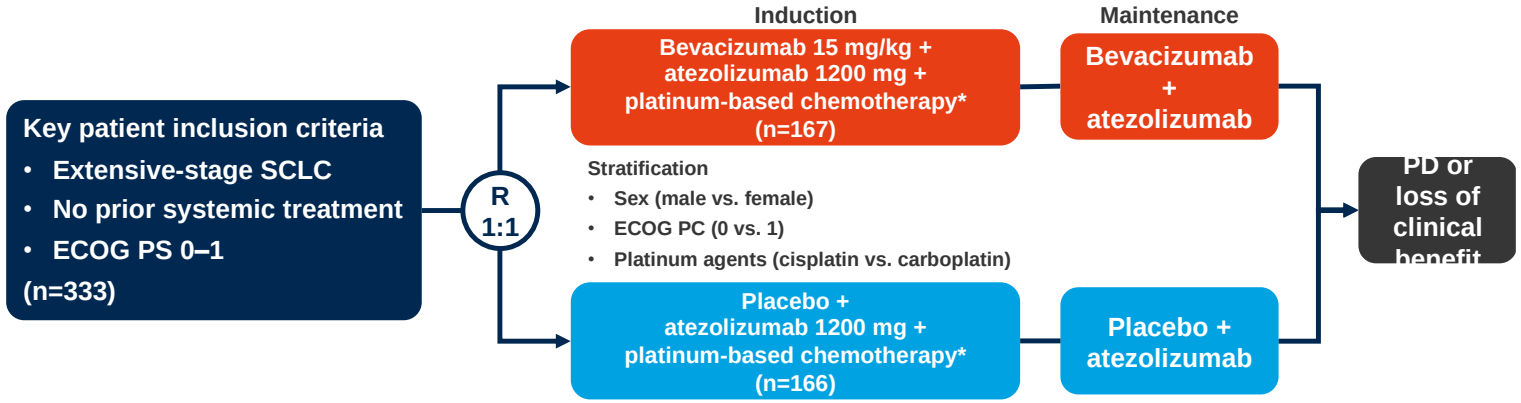


Interim OS: Primary Analysis Set



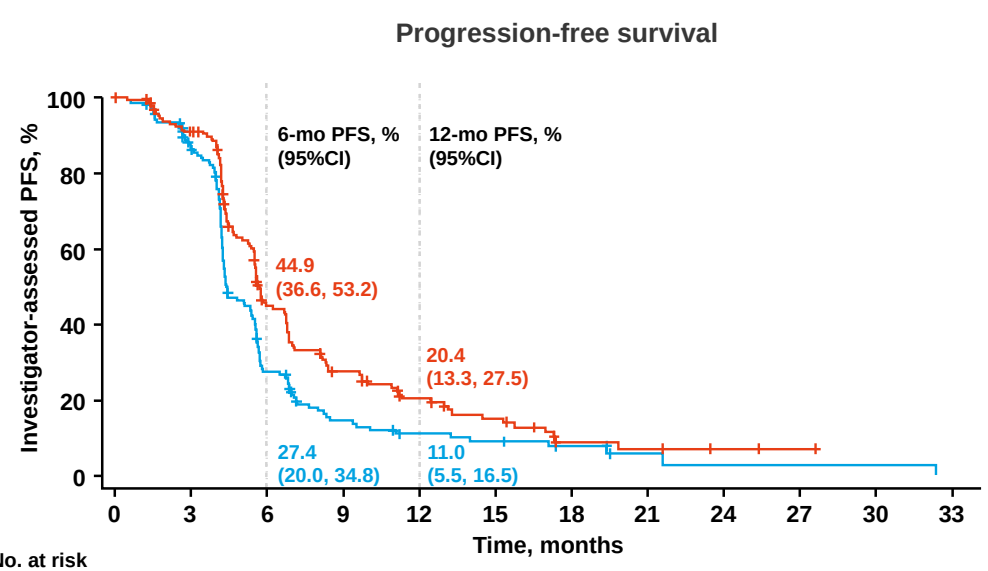
Rudin C, ASCO 2022

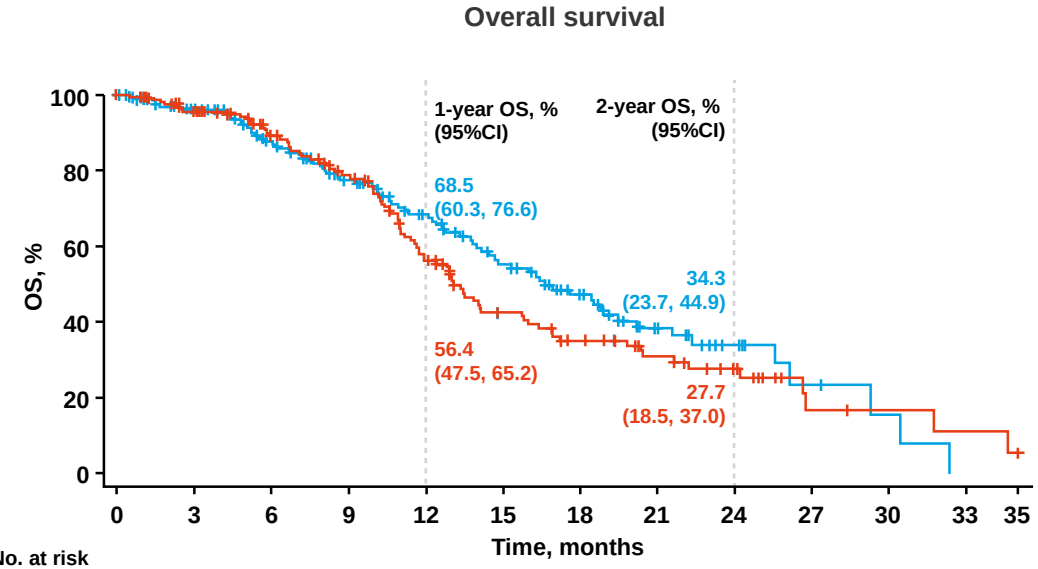
No benefit by adding anti-VEGF to standard CT-IO



Primary endpoint
- PFS (investigator-assessed)

Secondary endpoints
- OS, ORR, DoR, safety





Ohe Y et al. ASCO 2024

Benmelstobart (PD-L1 inhibitor) + Anlotinib (anti-VEGF) + CT vs CT: A Randomized, Double-blind, Phase III Trial (ETER701)

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)

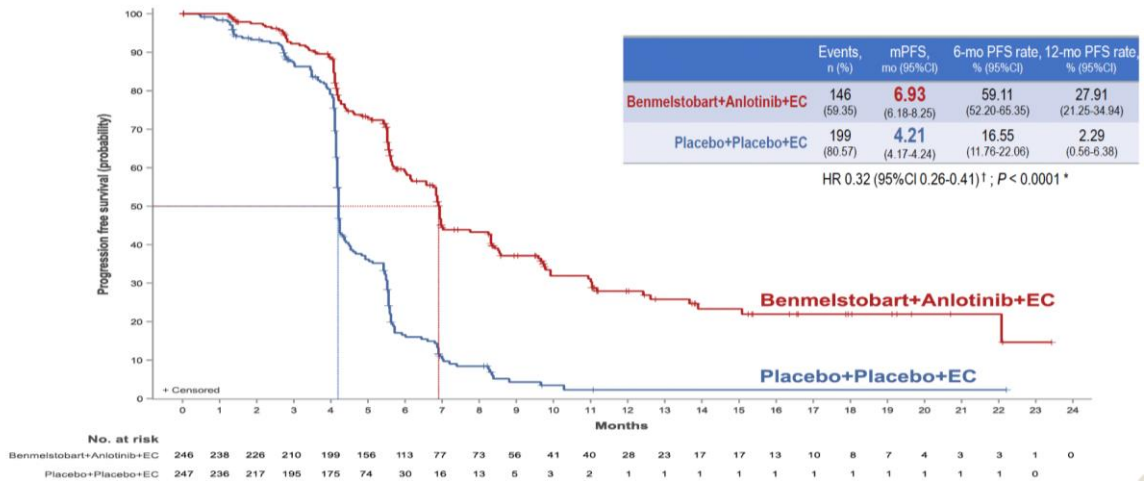
N=738

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

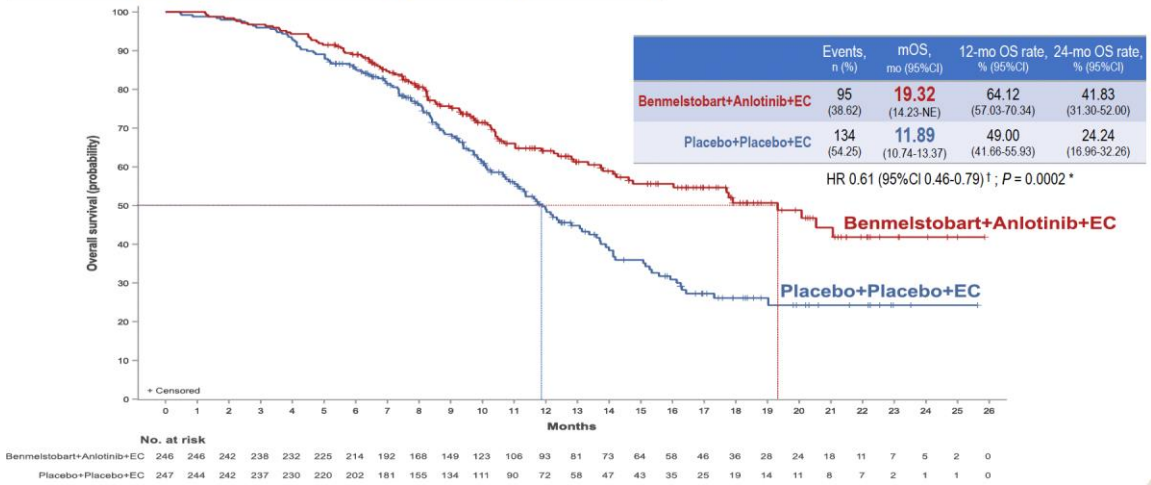
Primary Endpoint: PFS (ITT Population)



	Events, n (%)	mPFS, mo (95%CI)	6-mo PFS rate, % (95%CI)	12-mo PFS rate, % (95%CI)
Benmelstobart+Anlotinib+EC	146 (59.35)	6.93 (6.18-8.25)	59.11 (52.20-65.35)	27.91 (21.25-34.94)
Placebo+Placebo+EC	199 (80.57)	4.21 (4.17-4.24)	16.55 (11.76-22.06)	2.29 (0.56-6.38)

HR 0.32 (95%CI 0.26-0.41)† ; *P* < 0.0001 *

Primary Endpoint: OS (ITT Population)



	Events, n (%)	mOS, mo (95%CI)	12-mo OS rate, % (95%CI)	24-mo OS rate, % (95%CI)
Benmelstobart+Anlotinib+EC	95 (38.62)	19.32 (14.23-NE)	64.12 (57.03-70.34)	41.83 (31.30-52.00)
Placebo+Placebo+EC	134 (54.25)	11.89 (10.74-13.37)	49.00 (41.66-55.93)	24.24 (16.96-32.26)

HR 0.61 (95%CI 0.46-0.79)† ; *P* = 0.0002 *

ISG IRE

Cheng Y et al, WCLC 2023

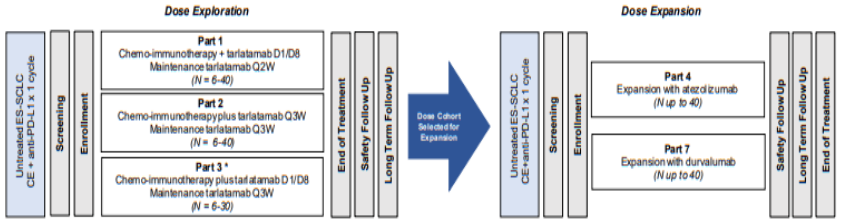
Potential strategies to improve disease control in 1^ line: maintenace trials

Phase 1:
Maintenance TARLATAMAB + IO

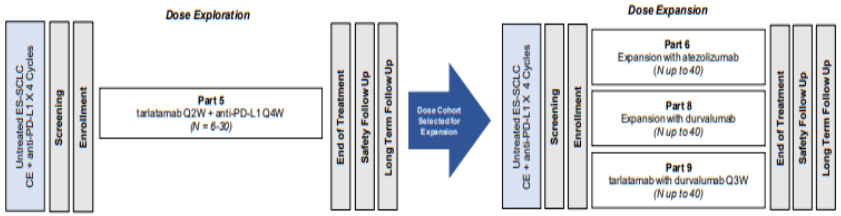
1.2 Study Schema

Figure 1-1. Overall Study Schema

Concomitant Chemo-Immunotherapy and Maintenance: Carboplatin, Etoposide, anti-PD-L1, and Tarlatamab



Maintenance Only: anti-PD-L1 and Tarlatamab



AMG 757 = tarlatamab; CE = carboplatin and etoposide; D = day; ES-SCLC = extensive stage small cell lung cancer; N = number of subjects; PD-L1 = programmed death ligand 1; Q2W = every 2 weeks; Q3W = every 3 weeks; Q4W = every 4 weeks
Tarlatamab D1/D8: tarlatamab initiates with step dosing in cycle 1 and then is given on day 1 and day 8 of a 21-day cycle
Tarlatamab Q2W: tarlatamab initiates with step dosing in cycle 1 and then is given on day 1 and day 15 of a 28-day cycle

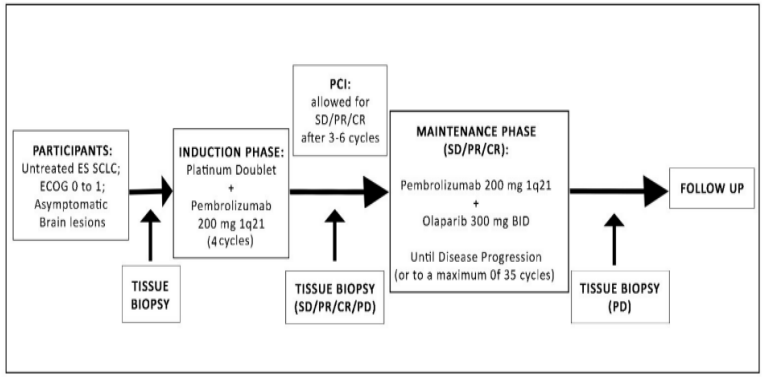
Phase 2:
Maintenance PARPi + IO

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Istituto Romagnolo per lo Studio dei Tumori "Dino Amadori"
Istituto di Ricovero e Cura a Carattere Scientifico

ISTITUTO ROMAGNOLO PER LO STUDIO DEI TUMORI DINO AMADORI

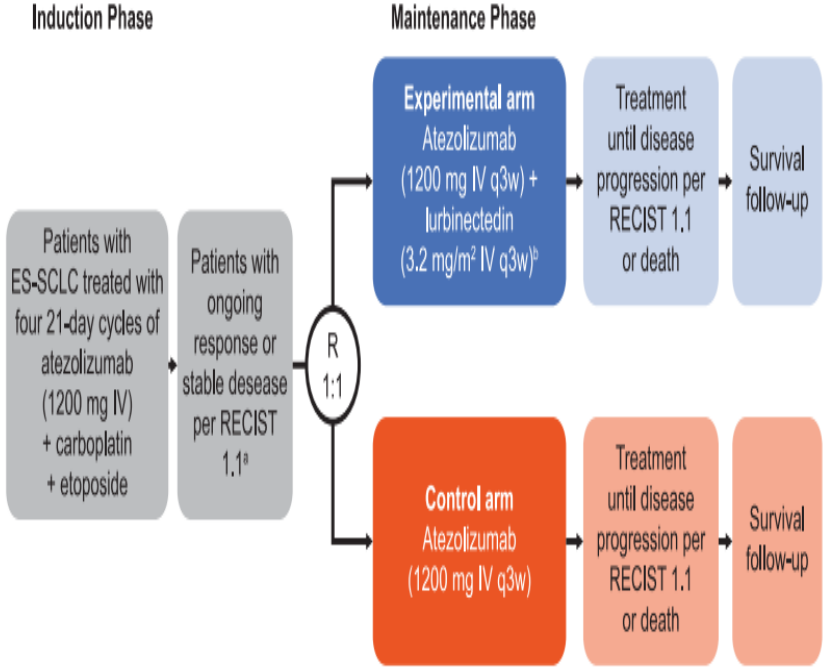
THOR

STUDY SCHEMA



Primary Endpoints: PFS
Secondary Endpoints: ORR, OS
Safety
Biological features

Phase 3:
Maintenance LURBINECTEDIN + IO



ES-SCLC, extensive stage small-cell lung cancer; q3w, once every 3 weeks; R, randomized; RECIST 1.1, Response Evaluation Criteria In Solid Tumors version 1.1.
[a]Following the induction therapy but before randomization, participants may receive prophylactic cranial irradiation at the investigator's discretion per local standard.
[b]Granulocyte colony-stimulating factor as primary prophylaxis is mandatory for participants assigned to the lurbinectedin-containing arm.

ISG IRE

Tarlatamab + (ATEZO/DURVA) as 1^Line Maintenance after for ES-SCLC: DeLLphi-303 Phase 1b Study

Key patient inclusion criteria
- Extensive-stage SCLC
- Any DLL3 status
- ECOG PS 0–1

(n=88)

→ **Platinum-etoposide + PD-L1 inhibitor (4–6 cycles)**

→ Non-PD

→ **Tarlatamab 10 mg IV q2w + atezolizumab 1680 mg IV q4w (n=48)**

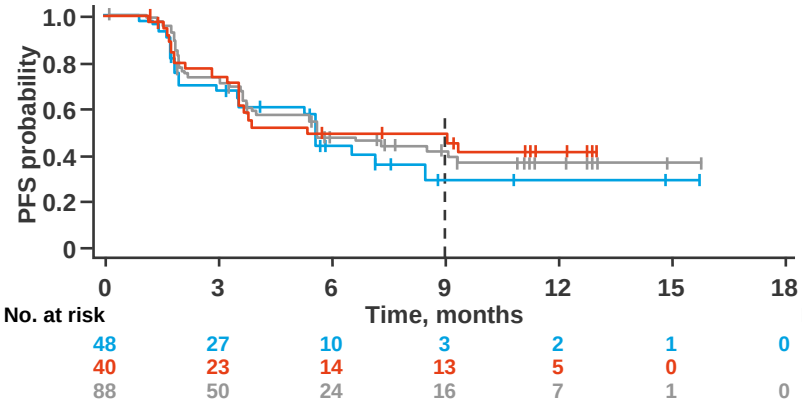
→ **Tarlatamab 10 mg IV q2w + durvalumab 1500 mg IV q4w (n=40)**

Primary endpoints
- Safety

Secondary endpoints
- PFS, OS, DCR

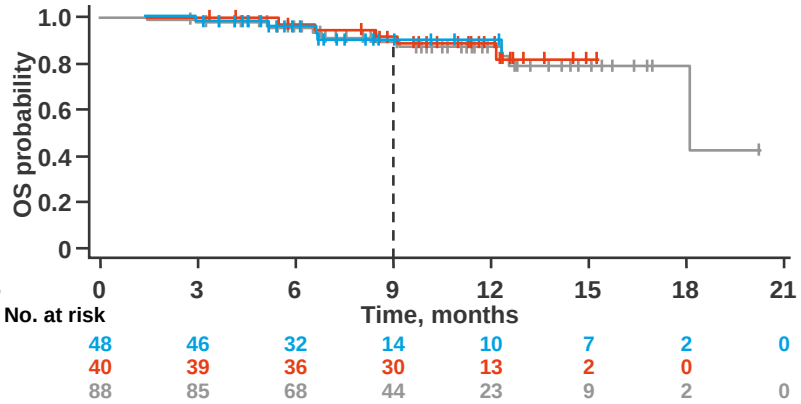
Progression-free survival (beginning from 1L maintenance)

	Tarlatamab + atezolizumab	Tarlatamab + durvalumab	Tarlatamab + IO (total)
mPFS, mo (95%CI)	5.6 (3.5, 8.5)	5.3 (3.5, NE)	5.6 (3.6, 9.0)
9-mo PFS, % (95%CI)	26.8 (11.1, 45.3)	47.5 (29.7, 63.3)	39.3 (27.3, 51.0)



Overall survival (beginning from 1L maintenance)

	Tarlatamab + atezolizumab	Tarlatamab + durvalumab	Tarlatamab + IO (total)
9-mo OS, % (95%CI)	86.7 (70.3, 94.4)	91.8 (76.6, 97.3)	88.9 (78.7, 94.3)



Tarlatamab + atezolizumab (mFU 7.4 mo (1.4–20.4)

Tarlatamab + durvalumab (mFU 11.5 (2.8, 15.5)

Tarlatamab + IO (total)

TRAEs, %	TARLA + ATEZO (n=48)	TARLA + DURVA (n=40)
Any	98	96
Grade ≥3		
CRS	2	0
Fatigue	2	0
Appetite decrease	2	0
Neutropenia	10	8
Lymphopenia	6	8

ISG IRE

Lau S et al. WCLC 2024

SCLC-ED relapsed: second lines scenario

Topotecan
ORR 2-11%
patinum-resistant
SCLC-ED

Fase	Farmaco	ORR	PFS	OS	Pubblicazione
2	**CAV**	18%	<3 mesi	-	Von Pawel et al. 1999
2	**Topotecano ev**	24%	3.1 mesi	-	Von Pawel et al. 1999
2	**Topotecano po**	18%	<3 mesi	-	EckardT et al. 2007
3	**Topotecano ev**	20%	4.3 mesi	8.6 mesi	Blackall et al. 2021
3	**Topotecan ev or CAV**	30%	4.0 mesi	7.6 mesi	Aix et al. 2023
2	**Lurbinectidina**	34%	3.9 mesi	9.3 mesi	Trigo et al. 2020
3	**Lurbinectedina + Doxorubicina**	32%	4.0 mesi	8.6 mesi	Aix et al. 2023
2	**Temozolamide + Velaparib**	39%	3.8 mesi	8.2 mesi	Pietanza el al. 2018
2	**Temozolamide + Olaparib**	41%	4.2 mesi	8.5 mesi	Farago et al. 2019
2	**Temozolamide + Talazoparib**	39%	4.5 mesi	11.9 mesi	Goldman et al. 2022
1	**Tarlatamb (dose escalation)**	23%	3.7 mesi	13.2 mesi	Paz-Ares et al. 2023
2	**Tarlatamb 10 mg/100 mg**	40/32%	4.9/3.9 mesi	14.3/NE mesi	Paz-Ares et al. 2023

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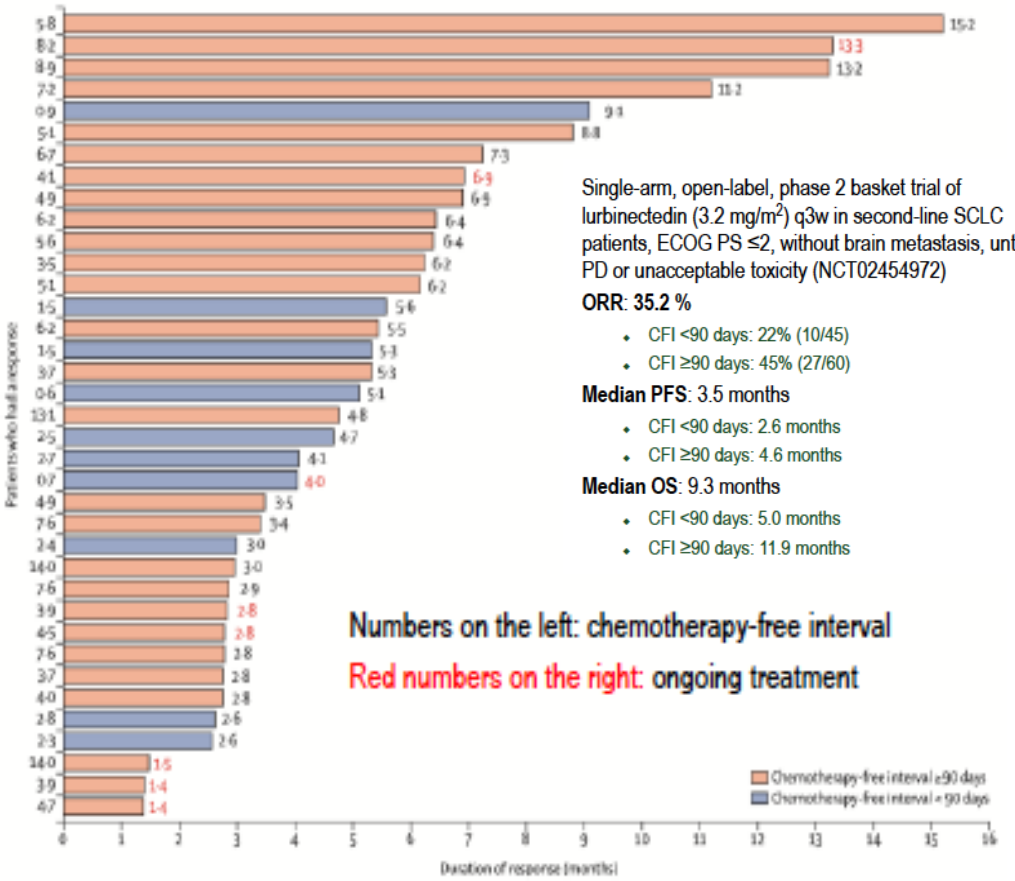
Relapsed SCLC-ED: Lurbinectidin (single agent or in combination)

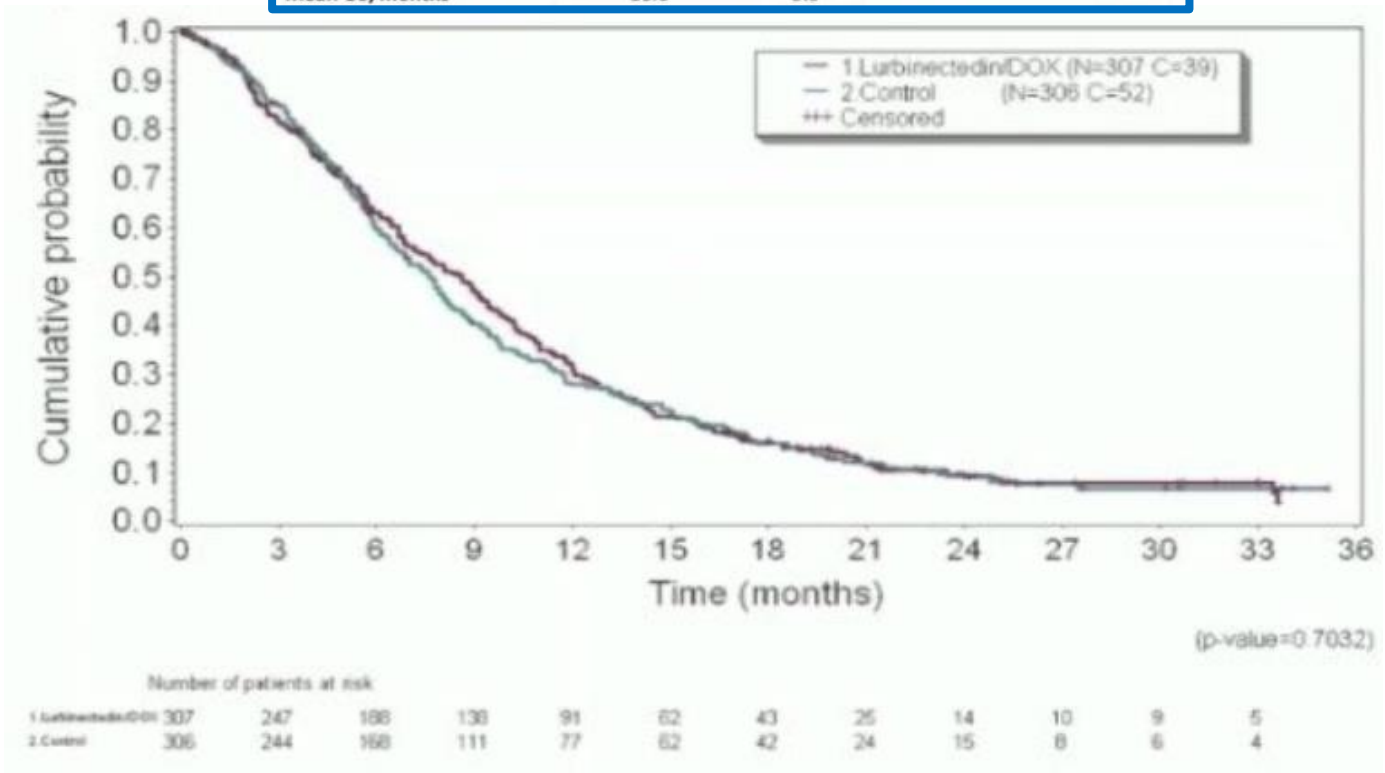
LURBI (mono)



CFI = chemotherapy-free interval

LURBI + DOXO

	Lurbinectedin+DOX (N=307)	Control (N=306)	Parameter	p-value
Events, n (%)	268 (87.3)	254 (83.0)		
Censored, n (%)	39 (12.7)	52 (17.0)		
Median OS (95% CI), months	8.6 (7.1, 9.4)	7.6 (6.6, 8.2)	HR : 0.967 (0.815, 1.148)	0.7032
Mean OS, months	10.6	9.9		



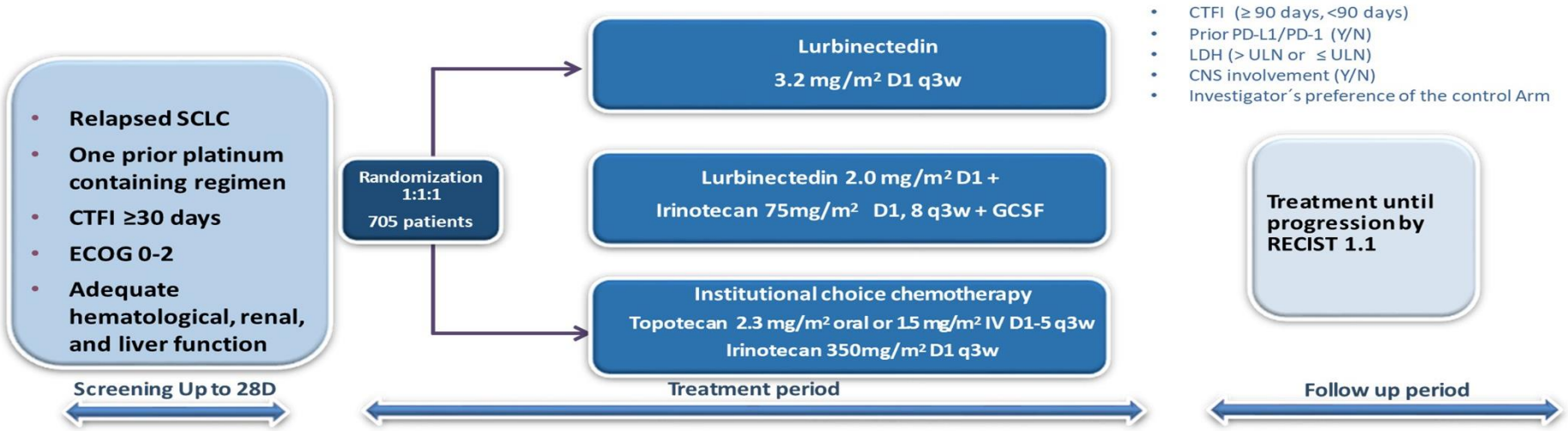
Trigo et al. Lancet Oncol 2020
Paz-Ares L et al. WCLC 2021
Aix et al. Lancet Resp Med 2023

Relapsed SCLC-ED: Lurbinectidin +/- Irinotecan

	All pts (n=101)	CTFI<90 d (n=52)	CTFI≥90 d (n=49)	CTFI>30 d (n=74)
ORR by IRC, % (95% CI)	43.6 (33.7-53.8)	25.0 (14.0-38.9)	63.3 (48.3-76.6)	52.7 (40.7-64.4)
DoR by IRC (mo), median (95% CI)	7.1 (4.6-9.4)	6.9 (3.9-7.6)	8.2 (4.4-12.4)	7.6 (4.6-9.7)
PFS by IRC (mo), median (95% CI)	4.7 (3.8-5.7)	3.3 (2.6-5.0)	5.7 (4.2-8.3)	5.0 (4.1-7.2)
OS (mo), median (95% CI)	9.6 (7.8-13.4)	7.5 (3.5-8.8)	14.0 (10.1-21.4)	12.7 (9.1-14.1)
OS rate at 12 mo, % (95% CI)	43.4 (33.4-53.4)	25.3 (13.2-37.5)	63.1 (49.1-77.2)	52.0 (40.3-63.8)

CI, confidence interval; CTFI, chemotherapy-free interval; d, days; DoR, duration of response; mo, months; ORR, overall response rate; OS, overall survival; PFS, progression free survival.

Phase 2
LURBI+IRI
«expantion cohort»

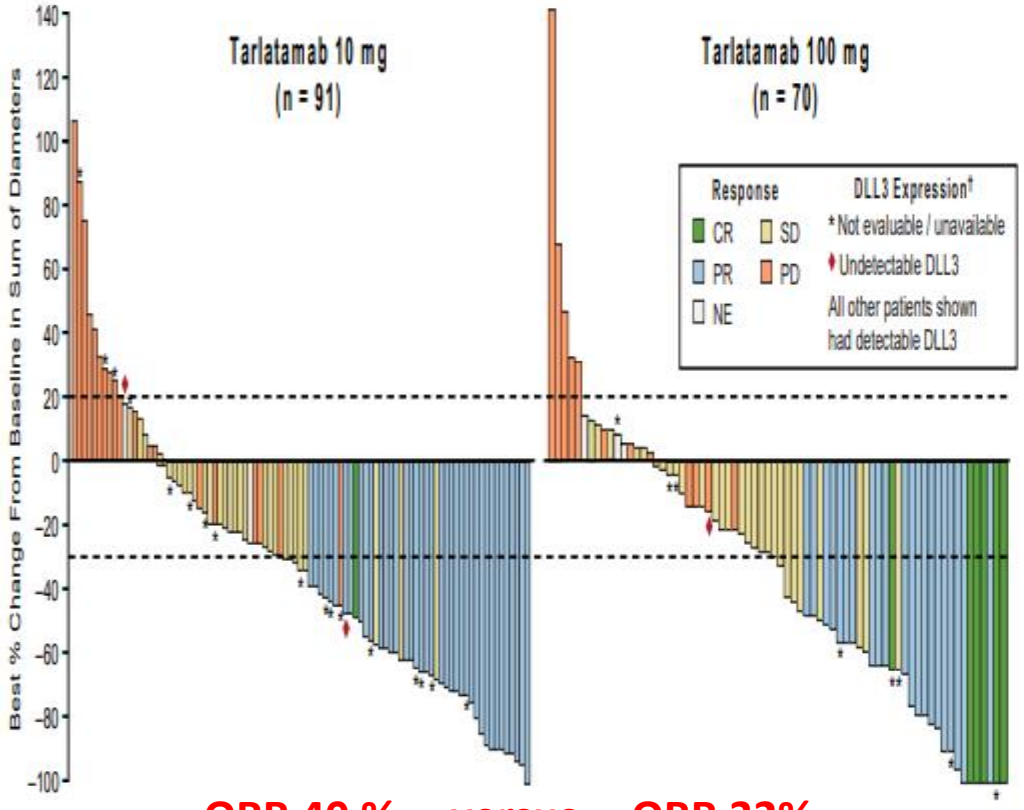


Phase 3
LURBI+/-IRI vs TOPO
LAGOON Trial
ongoing

Endpoints
- **Primary Endpoint:** Overall Survival
- **Secondary**: PFS, ORR, DoR, Safety, PRO

Paz-Ares L et al. ESMO 2024

Phase 2 of DLL3-Targeted T-cell Engager Tarlatamab in SCLC
DeLLphi-301 Efficacy Data

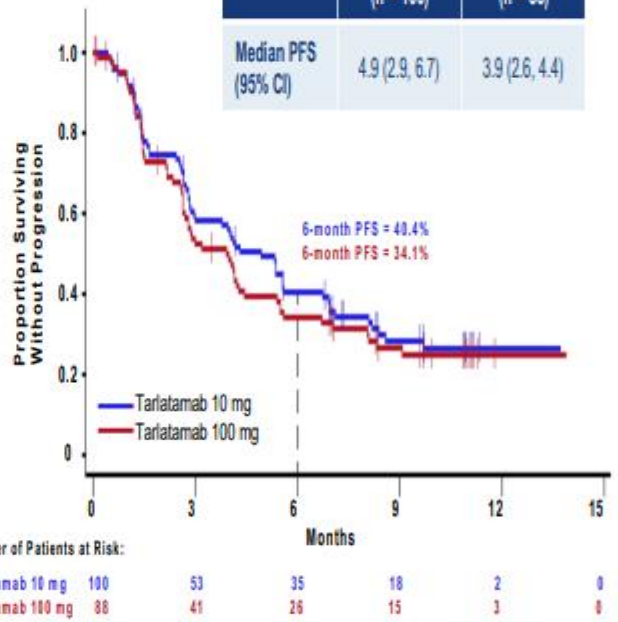


ORR 40 % versus ORR 32%

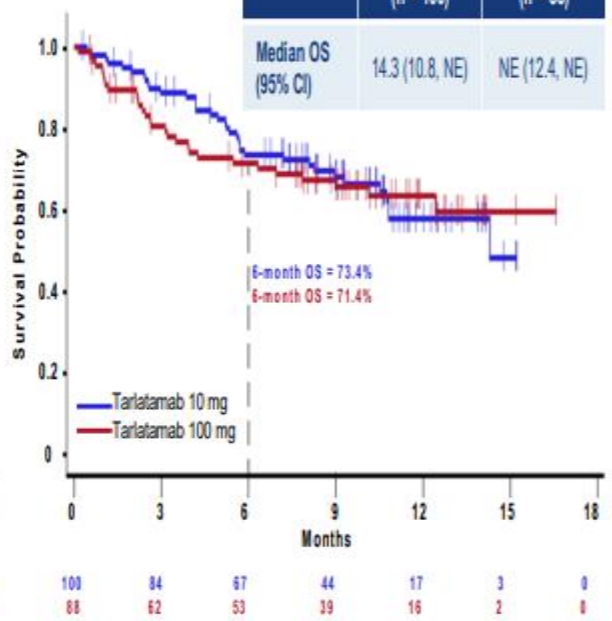
PFS and OS

Among patients with an ORR,
DoR was at least 6 months in 59%

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



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



No. of previous lines of therapy — no. (%)			
1	2 (2)	0	2 (2)
2	65 (65)	22 (65)	48 (55)
3	19 (19)	6 (18)	22 (25)
>3	14 (14)	6 (18)	16 (18)
Median no. of previous lines of therapy (range)	2.0 (1–6)	2.0 (2–6)	2.0 (1–8)

Paz-Ares et al. ESMO e NEJM 2023

Phase 2 of DLL3-Targeted T-cell Engager Tarlatamab in SCLC
DeLLphi-301 SAFETY DATA

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**

*The safety analysis set includes Part 1, Part 2, and Part 3 who received at least 1 dose of tarlatamab (N = 220). †Fatal TRAE was respiratory failure. **CRS**, cytokine release syndrome; **TEAE**, treatment emergent adverse event.

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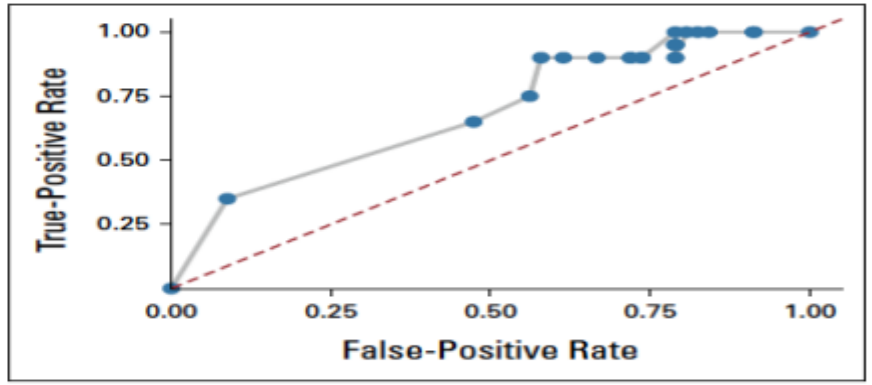
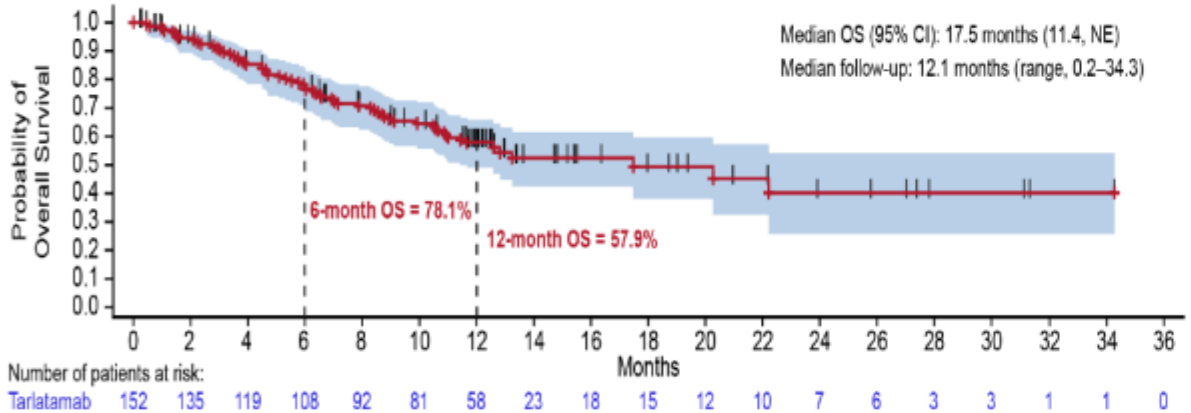
Paz-Ares et al. ESMO e NEJM 2023

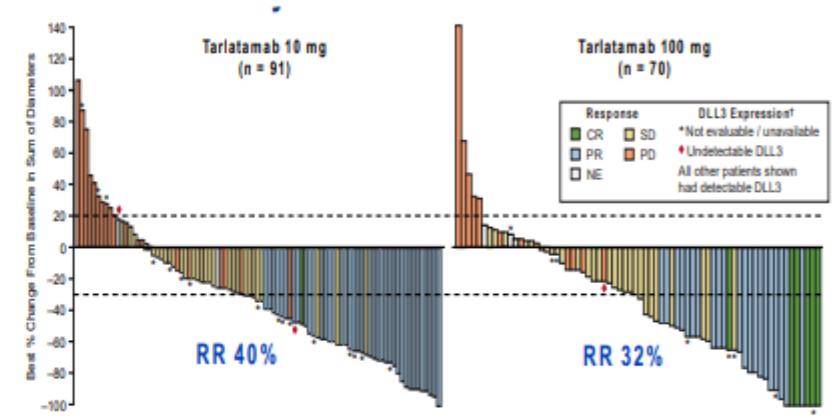
Who is benefitting and how much?

- No clear biomarkers of benefit as yet
- DLL3 expression is not a major predictor
- Not all benefit is driven by response:



carry-over effect





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

HD Hummel et al., ELCC 2024

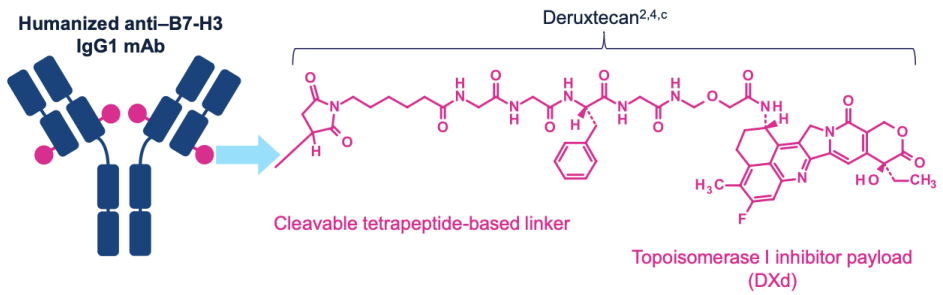
Paz-Ares JCO 2022 & NEJM 2023

ISG IRE

Ifinatamab Deruxtecan (I-DXd) in ES-SCLC: Interim Analysis (IDeate-Lung01)

I-DXd is a B7-H3 (CD276)–directed ADC with 3 components[1–4]:

- A humanized anti–B7-H3 IgG1 mAb
- A tetrapeptide-based cleavable linker that covalently bonds antibody and payload
- A topoisomerase I inhibitor payload (an exatecan derivative, DXd)



Key patient inclusion criteria

- Extensive-stage SCLC
- ≥1 prior line of platinum-based chemotherapy and ≤3 prior lines of systemic therapy
- Progression on or after most recent systemic therapy
- Asymptomatic brain metastases permitted
- ECOG PS 0–1

(n=88)

R 1:1

- Ifinatamab deruxtecan 8 mg/kg q3w (n=46)
- Ifinatamab deruxtecan 12 mg/kg q3w (n=42)

Stratification
- 2L chemotherapy treatment-free interval (<90 vs. ≥90 days), 2L or 3L
- Prior anti-PD-(L)1 (yes vs. no)

Extended enrollment at RP3D (n≈70 3L+)

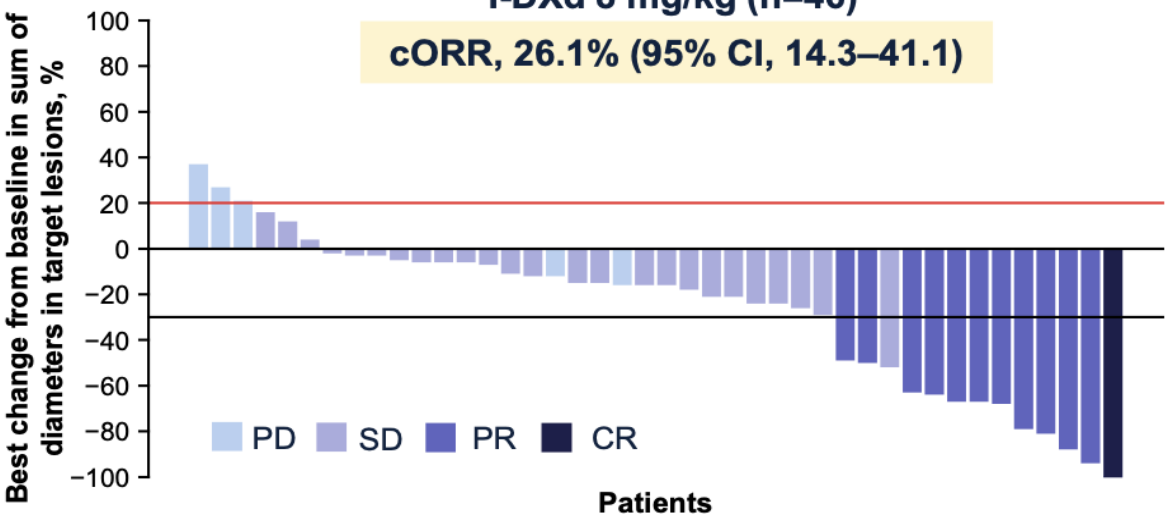
Primary endpoint
- ORR (BICR)

Secondary endpoints
- DoR, PFS, OS, DCR, TTR, PK, safety

Exploratory endpoint
- Intracranial ORR

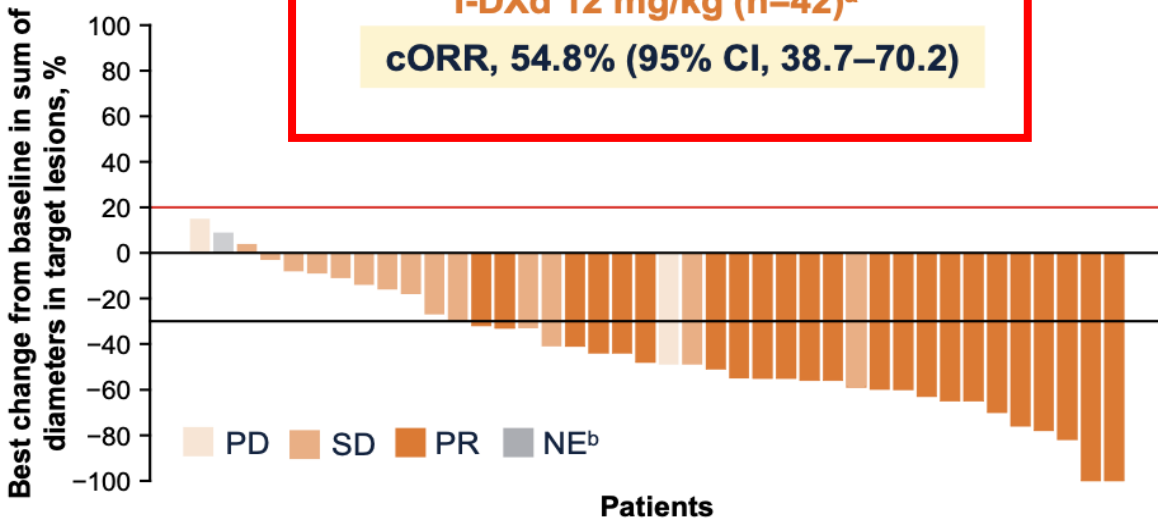
I-DXd 8 mg/kg (n=46)[a]

cORR, 26.1% (95% CI, 14.3–41.1)



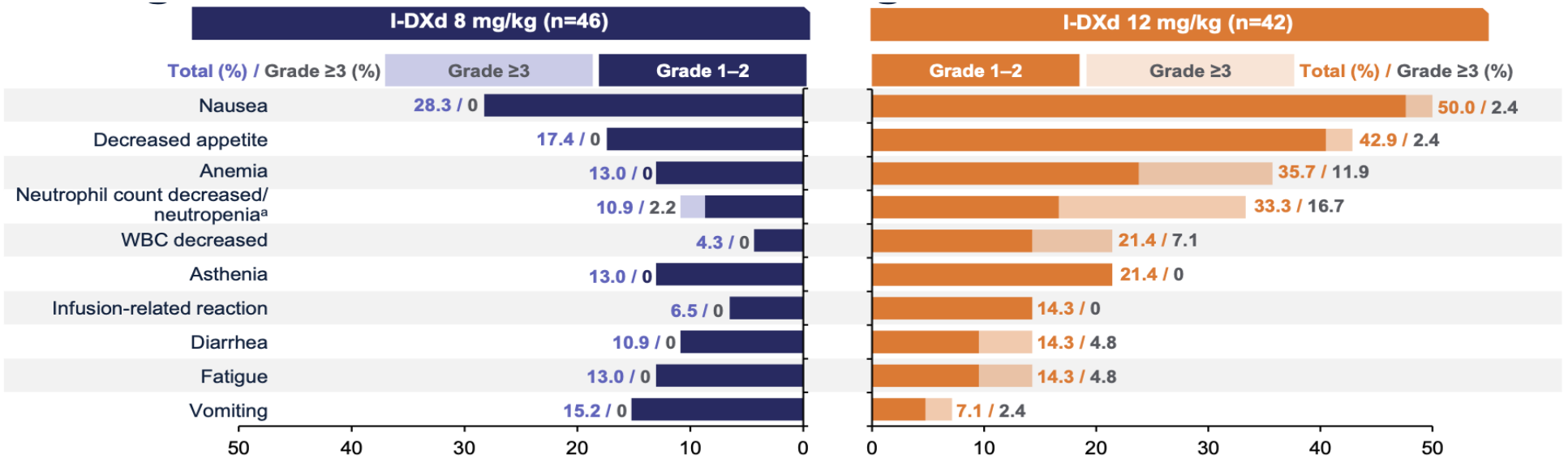
I-DXd 12 mg/kg (n=42)[a]

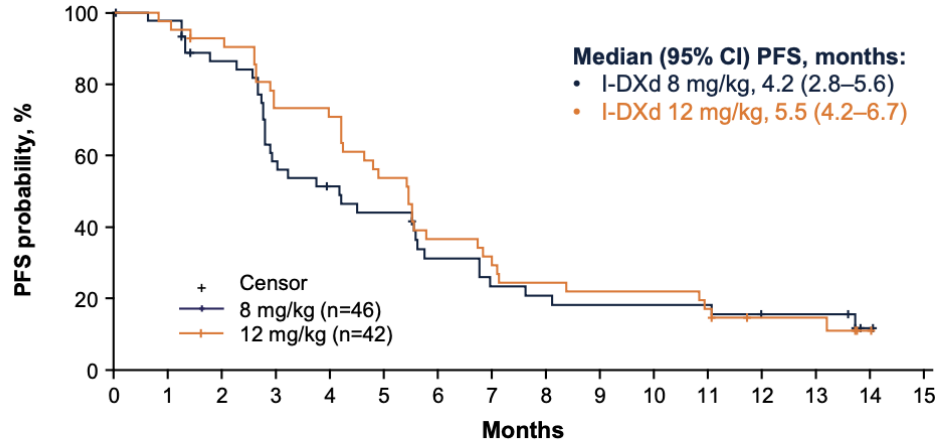
cORR, 54.8% (95% CI, 38.7–70.2)

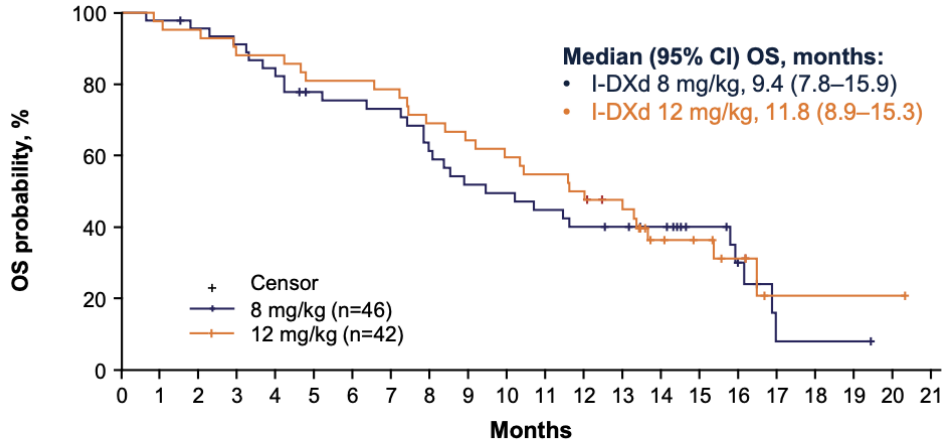


Rudin CM et al. WCLC 2024

Ifinatamab Deruxtecan (I-DXd) in ES-SCLC: Interim Analysis (IDeate-Lung01)







Number of patients still at risk

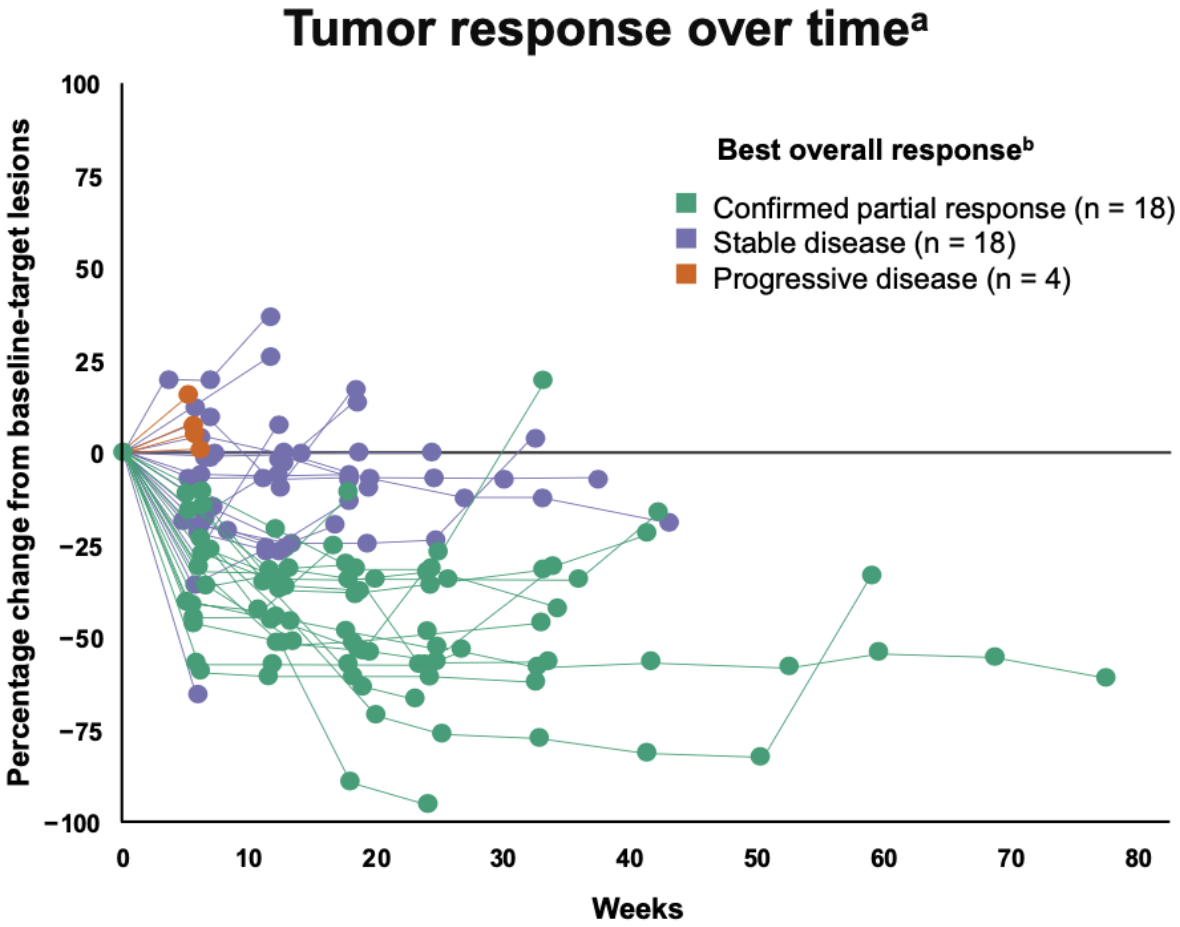
8 mg/kg	46	44	37	25	21	18	12	9	8	7	7	7	5	5	1	0
12 mg/kg	42	41	38	30	29	22	15	12	10	9	9	7	4	4	1	0

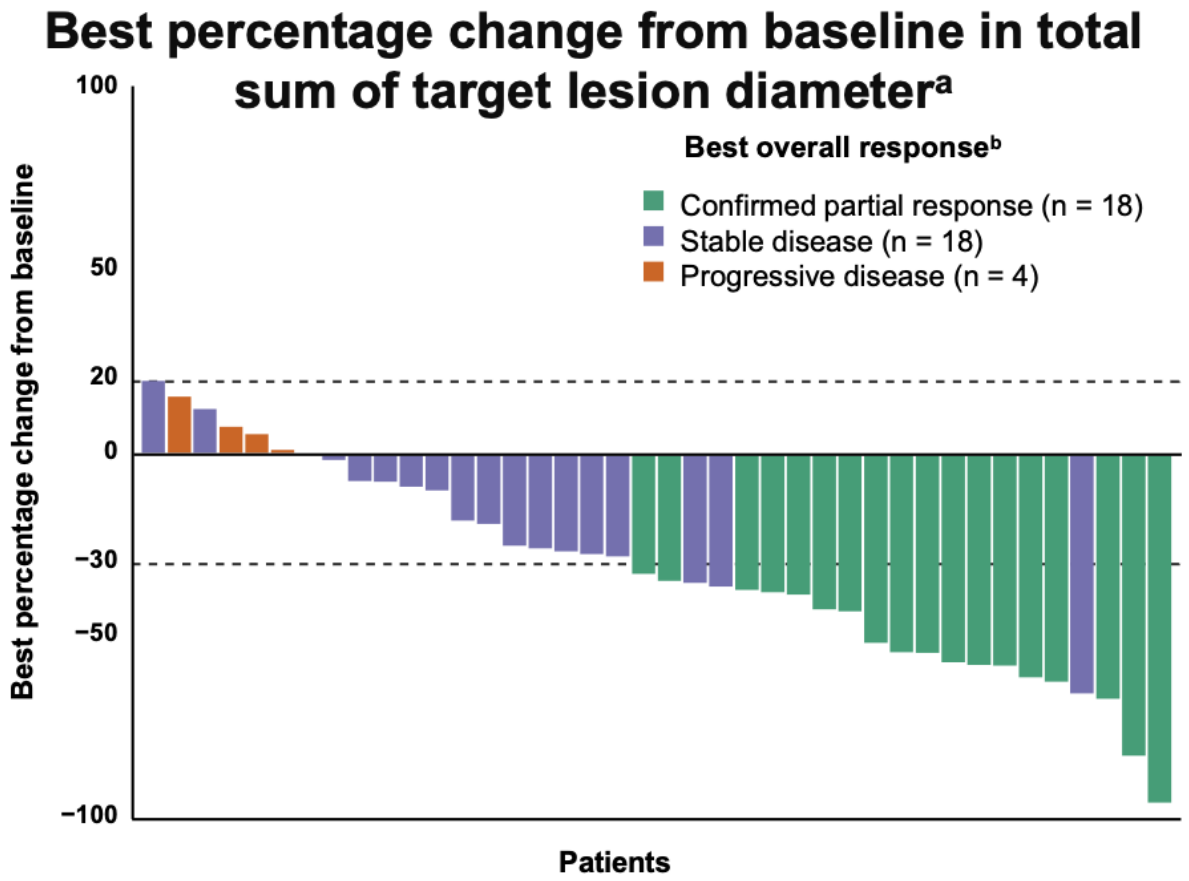
Number of patients still at risk

8 mg/kg	46	45	43	41	37	33	32	31	26	22	21	19	17	16	14	9	5	1	1	1	0	0
12 mg/kg	42	41	40	37	37	34	34	33	29	27	25	23	20	17	10	8	5	1	1	1	1	0

Rudin CM et al. WCLC 2024

Sacituzumab Govitecan (TROP2 Targeted ADC) as II line in ES-SCLC

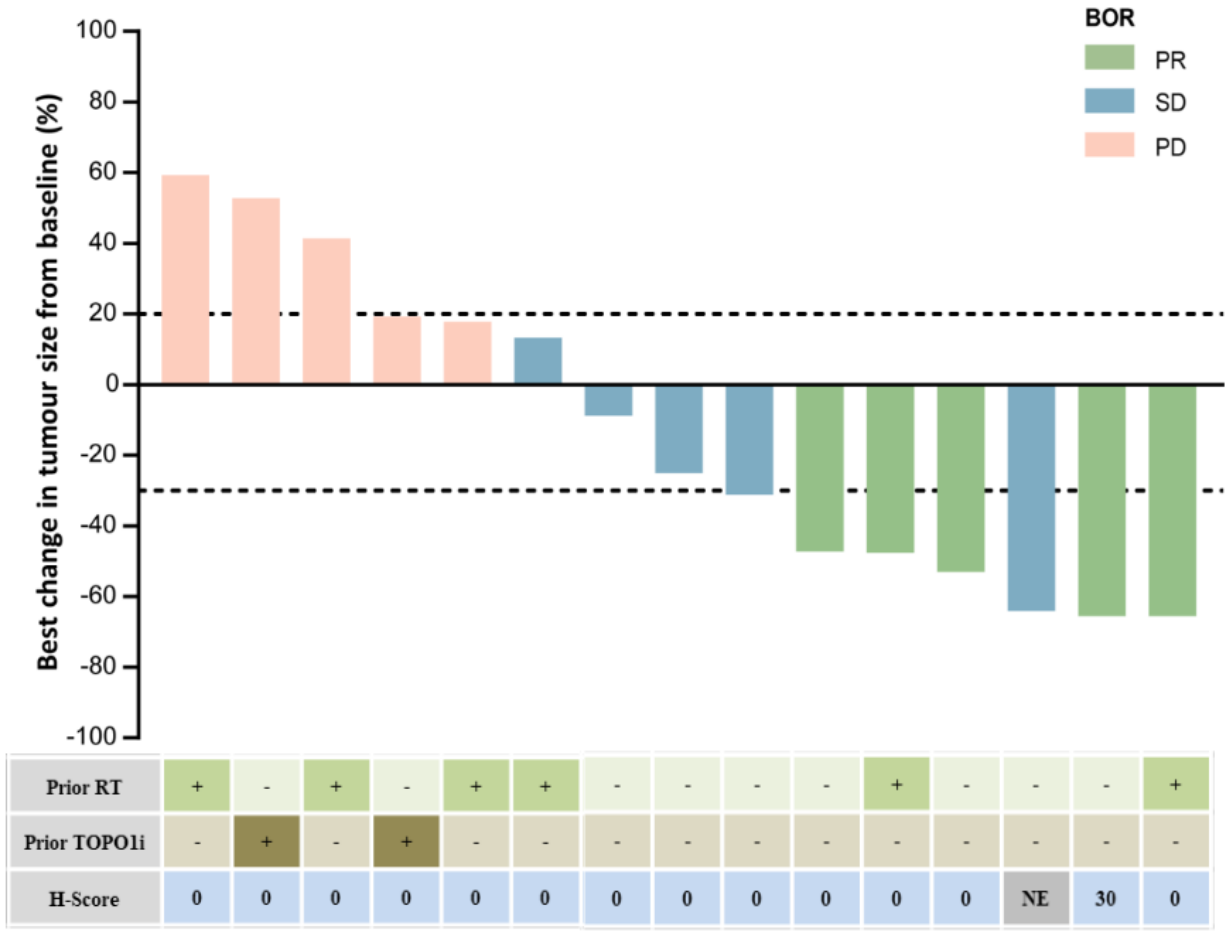


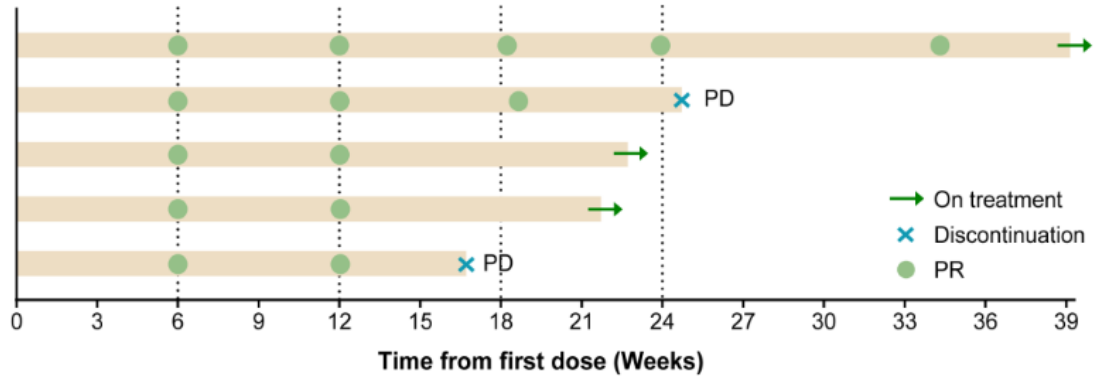


- 76.7% (33/43) of patients had tumor shrinkage
- 48.8% (21/43) of patients had a reduction of >30% in target lesion diameter

Dowlati A et al. WCLC 2024

SHR-A1921 (TROP-2 Targeted ADC) as II line in ES-SCLC





	SCLC cohort (N=17)
Evaluable, N	15
BOR, n (%)	
PR	5 (33.3)
SD	5 (33.3)
PD	5 (33.3)
ORR, % (95% CI)	33.3 (11.8-61.6)
DCR, % (95% CI)	66.7 (38.4-88.2)
DoR, months (95% CI)	4.4 (2.3-NR)

Wang J et al. WCLC 2024

CONCLUSIONS

- **Consolidation IO (DURVA) will be a new gold standard after CT/RT in LS-SCLC**
- **Front-line treatment is at the moment the unique chance to prolong survival in ED-SCLC**
- CT-IO modestly but significantly prolongs survival in advanced SCLC
- Combination of PE and IO (ATEZO or DURVA) is our standard of care
- Chemotherapy with PE as standard option, if IT contraindicated
- Few options currently available for second and subsequent lines therapy
- Participation in clinical trials strongly recommended (new agents: BiTE, new CT combination, ADC, etc.)
- New molecular classification of SCLC potentially helpful in identifying the immune-sensitive population

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