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Treatment of SCLC in 2024: Where are we at?

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MaTOS
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LS SCLC: Management

STAGE I-IIA

- **~5% of SCLC have Stage I-IIA (T1-2aN0) disease**
- Lobectomy followed by mediastinal lymph node dissection
- If surgery is not an option consider SABR
- **Adjuvant chemotherapy** is recommended
- Consider adjuvant radiation if LN +
- Retrospective series: **39-86% 5 yr OS**

STAGE IIB-III

Concurrent chemoradiotherapy followed by ICI

- Etoposide/Cisplatin or carboplatin x 4 cycles
- Radiation: BID or qD
  - ➢ **Consolidation durvalumab – new in 2024**

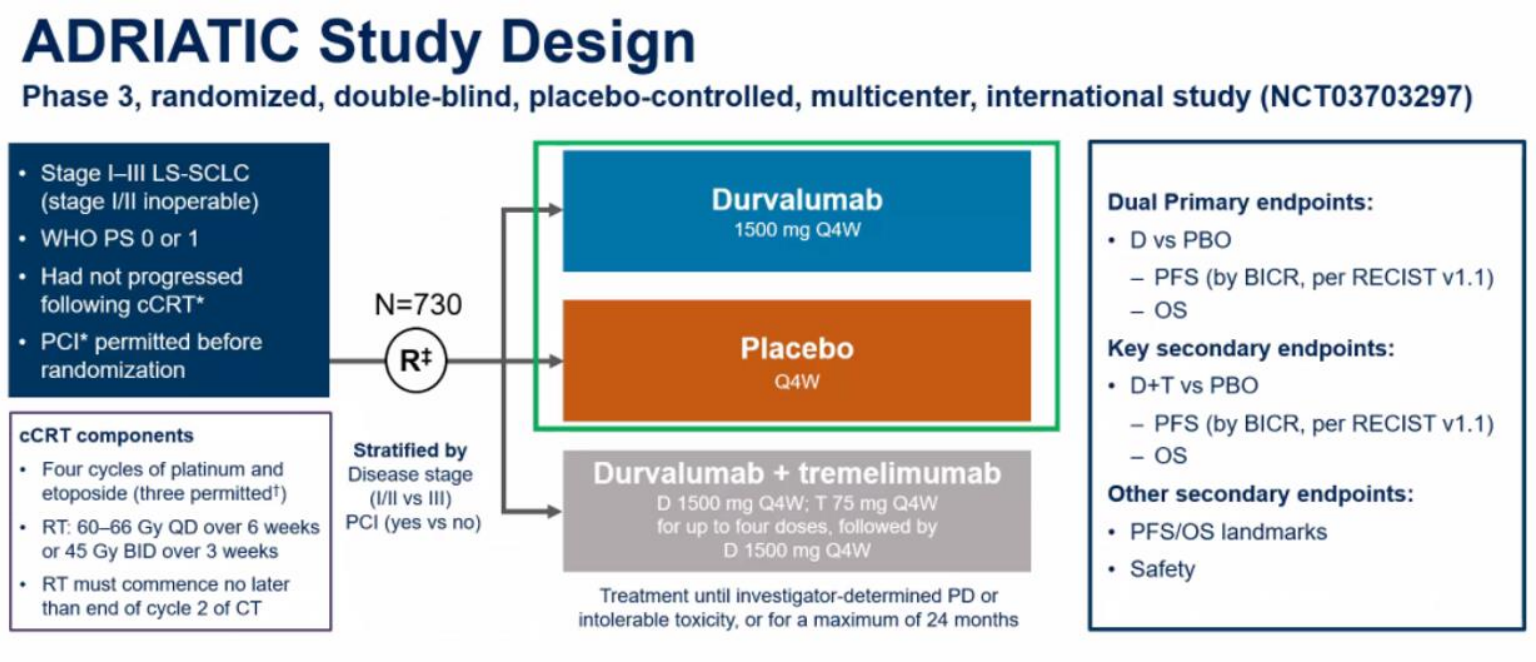
- Prophylactic Cranial Irradiation (PCI)
  - 3 year survival benefit

Key Studies of TRT in LS SCLC

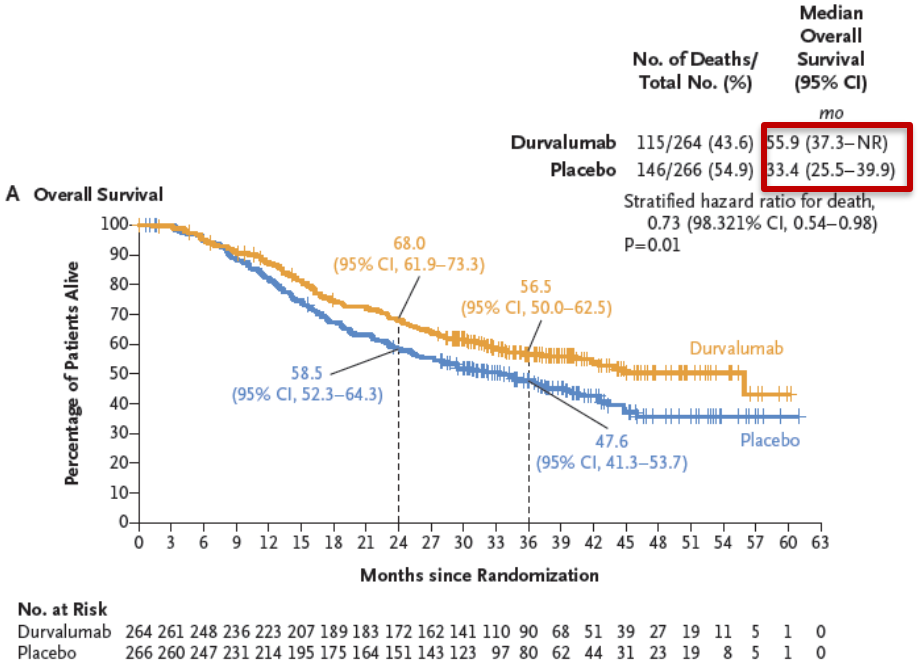
Trial	Phase	N	Arms	mOS (mos)	5 yr OS	2 yr OS	G3/4 esophagitis
Randomized Phase 3 studies							
Intergroup 0096	3	417	**45Gy BID** 45Gy qD	23 19	26% 16%		32% 16%
CONVERT	3	547	45Gy BID 66Gy qD	30 25	34% 31%		19% 19%
CALGB 30610	3	638	45Gy BID 70Gy qD	28.5 30.5	29% 34%	58% 56%	17% 19%
Randomized Phase 2							
Gronberg	2	170	45Gy BID 60Gy BID	22.6 43.5	28.4% 41.6%	48% 74%	18.2% 21.2%

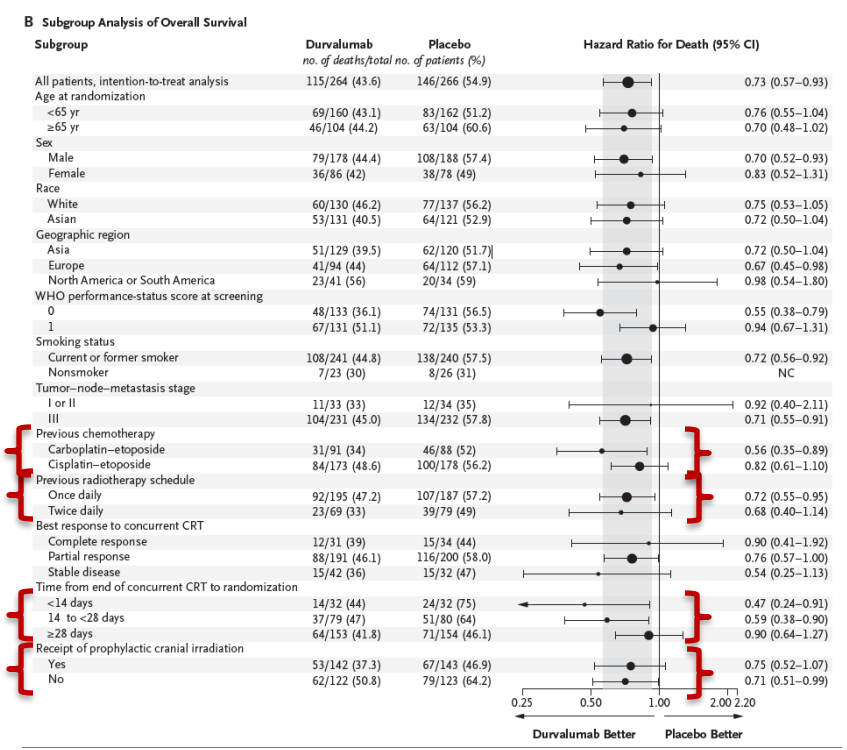
Turrisi AT III et al. *N Engl J Med*. 1999; Favre-Finn et al., *Lancet Oncology* 2017; Gronberg 2021 Lancet Oncology; Gronberg BH ASCO 2023 Meeting

ADRIATIC: Consolidation ICI after chemoRT is the new SOC



ADRIATIC Study: Improvement in mOS and mPFS with durvalumab consolidation



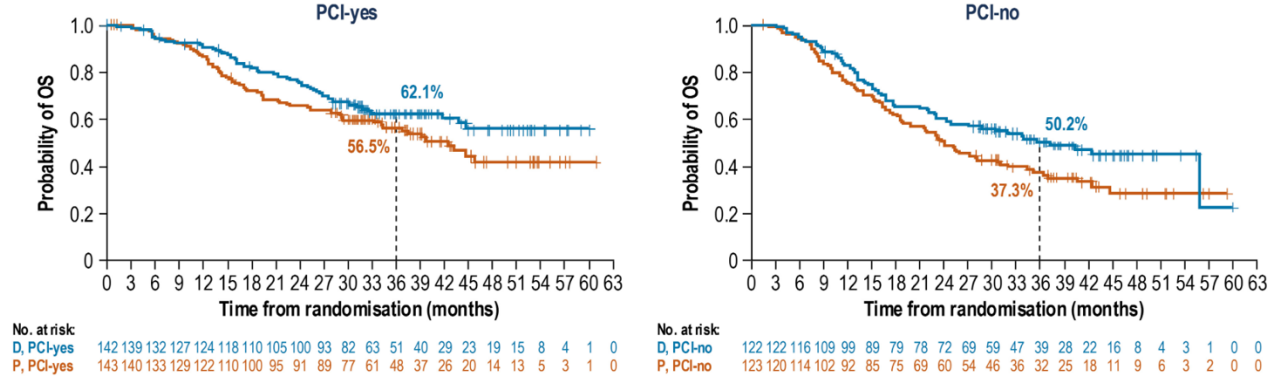


Cheng et al, NEJM 2024 - *DOI: 10.1056/NEJMoa2404873*, Senan S et al., Ann Oncol 2024; 35 (Suppl): LBA81

ADRIATIC: PCI subgroup analysis

PCI-Yes and PCI-No Subgroups – OS

	PCI-yes		PCI-no		ITT	
	D (n = 142)	P (n = 143)	D (n = 122)	P (n = 123)	D (n = 264)	P (n = 266)
Median OS (95% CI), months	NR (43.9–NE)	42.5 (33.4–NE)	37.3 (24.3–NE)	24.1 (18.8–31.1)	55.9 (37.3–NE)	33.4 (25.5–39.9)
3-year OS, %	62.1	56.5	50.2	37.3	56.5	47.6
HR (95% CI)	0.75 (0.52–1.07)*		0.71 (0.51–0.99)*		0.73 (0.57–0.93)†	
Multivariable HR (95% CI)	0.72 (0.50–1.03)‡		0.73 (0.52–1.02)‡		–	



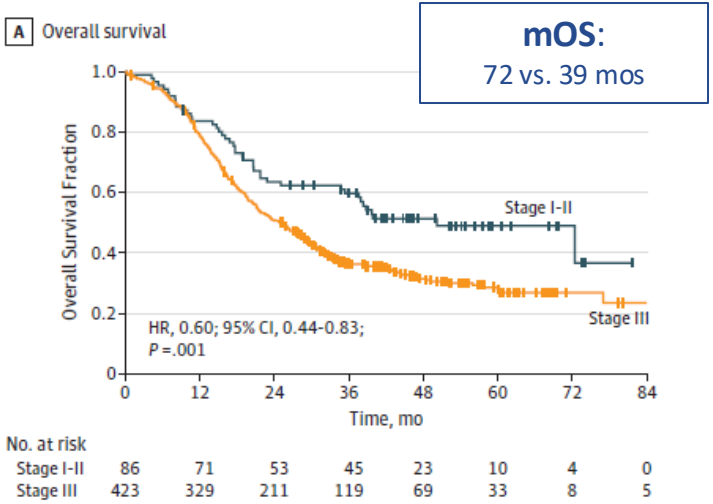
CI, confidence interval; NE, not estimable; NR, not reached; yr, year.

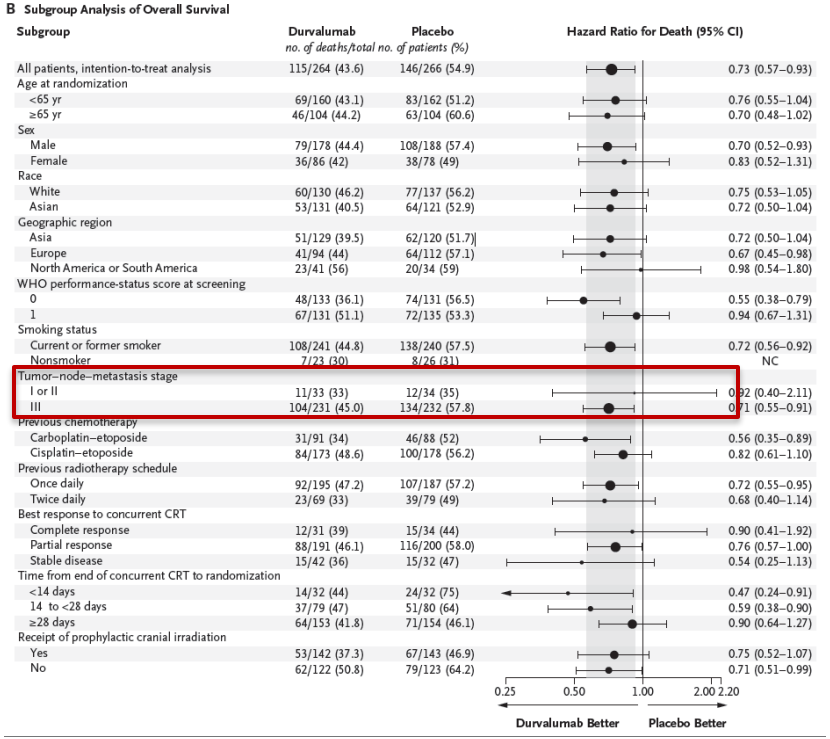
*Subgroup HRs and CIs calculated using an unstratified Cox proportional hazards model.†ITT HR and CIs calculated using a Cox proportional hazards model stratified by receipt of PCI.‡Multivariable analysis interaction p-value 0.96.

ADRIATIC Study: Subgroup analysis – patients with Stage I/II disease did not derive same benefit

CONVERT Study- secondary analysis:

- Phase 3 study of 45Gy BID vs 66Gy qD TRT with EP
- Outcomes of Stage I-II vs Stage III patients
    - 509 of 543 patients were eligible for analysis



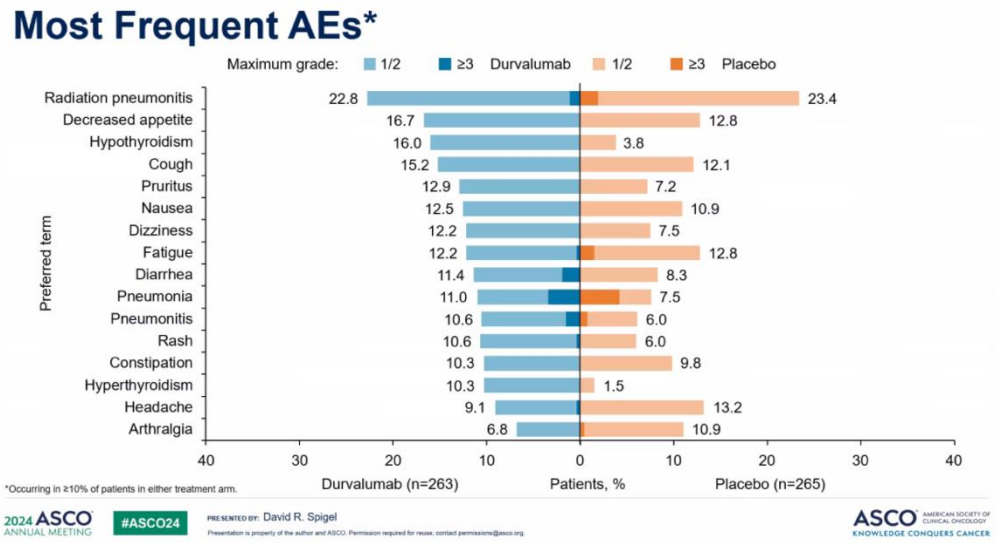


Cheng et al, NEJM 2024 - *DOI: 10.1056/NEJMoa2404873*, Senan S et al., Ann Oncol 2024; 35 (Suppl): LBA81; Salem et al., JAMA Oncol 2019

ADRIATIC: Adverse Events

Table 3. Adverse Events (Safety Population).*

Event	Durvalumab (N=262)†		Placebo (N=265)	
	Any Grade	Grade 3 or 4‡	Any Grade	Grade 3 or 4‡
	number of patients (percent)			
Any adverse event of any cause	247 (94.3)	64 (24.4)	234 (88.3)	64 (24.2)
Any serious adverse event, including events with outcome of death	78 (29.8)	—	64 (24.2)	—
Any adverse event with outcome of death§	7 (2.7)	—	5 (1.9)	—
Any event leading to discontinuation of durvalumab or placebo	43 (16.4)	—	28 (10.6)	—
Any event leading to dose interruption	91 (34.7)	—	76 (28.7)	—
Any immune-mediated adverse event¶	84 (32.1)	14 (5.3)	27 (10.2)	4 (1.5)
Common adverse events occurring at any grade in ≥10% or at a maximum severity of grade 3 or 4 in ≥1% of patients in either group				
Radiation pneumonitis	60 (22.9)	3 (1.1)	62 (23.4)	5 (1.9)
Decreased appetite	44 (16.8)	0	34 (12.8)	0
Hypothyroidism	42 (16.0)	0	10 (3.8)	0
Cough	40 (15.3)	0	32 (12.1)	0
Pruritus	34 (13.0)	0	19 (7.2)	0
Nausea	33 (12.6)	0	29 (10.9)	0
Dizziness	32 (12.2)	0	20 (7.5)	0
Fatigue	32 (12.2)	1 (0.4)	34 (12.8)	4 (1.5)
Diarrhea	29 (11.1)	5 (1.9)	22 (8.3)	0
Pneumonia	29 (11.1)	7 (2.7)	20 (7.5)	9 (3.4)
Pneumonitis	28 (10.7)	3 (1.1)	16 (6.0)	2 (0.8)
Rash	28 (10.7)	1 (0.4)	16 (6.0)	0
Constipation	27 (10.3)	0	26 (9.8)	0
Hyperthyroidism	27 (10.3)	0	4 (1.5)	0
Headache	24 (9.2)	1 (0.4)	35 (13.2)	0
Anemia	23 (8.8)	3 (1.1)	16 (6.0)	3 (1.1)
Arthralgia	18 (6.9)	0	29 (10.9)	1 (0.4)
Hyperglycemia	11 (4.2)	3 (1.1)	10 (3.8)	0
Hypertension	9 (3.4)	3 (1.1)	4 (1.5)	0
Lipase increased	8 (3.1)	5 (1.9)	7 (2.6)	4 (1.5)
Amylase increased	7 (2.7)	3 (1.1)	3 (1.1)	0
Chronic obstructive pulmonary disease	6 (2.3)	1 (0.4)	7 (2.6)	4 (1.5)
Pulmonary embolism	6 (2.3)	5 (1.9)	4 (1.5)	3 (1.1)
Pneumonitis or radiation pneumonitis‖	100 (38.2)**	8 (3.1)	80 (30.2)	7 (2.6)
Pneumonitis or radiation pneumonitis leading to discontinuation of durvalumab or placebo	23 (8.8)	—	8 (3.0)	—



LS SCLC – ongoing trials

Trial	No.	Type	ICI	Setting	Estimated Completion Date
DOLPHIN	NCT04602533	Phase II, Germany	Durvalumab	Frontline with CCRT	September 2023
Huang et al	NCT05034133	Phase II, China	Durvalumab	Frontline with chemotherapy, sequential XRT	August 2024
ADRIATIC	NCT03703297	Phase III, multinational	Durvalumab ± tremelimumab	Consolidation after CCRT	September 2024
NRG-LU005	NCT03811002	Phase III, United States + Japan	Atezolizumab	Frontline with CCRT	December 2026
SURPASS	NCT05623267	Phase II/III, China	Sugemalimab	Consolidation after CCRT	March 2027
ACHILES	NCT03540420	Phase II, multinational	Atezolizumab	Consolidation after CCRT	April 2027
KEYLYNK-013	NCT04624204	Phase III, multinational	Pembrolizumab	Frontline with CCRT, then with olaparib	October 2027

Study	NCT	Phase	Clinical Setting	Treatment arms	Primary Endpoint
DeLLphi-305	NCT06211036	III	ES SCLC after chemoIO induction	Durvalumab vs Durvalumab plus Tarlatamab	OS
RADIATION					
MAVERICK	NCT04155034	III	LS SCLC or ES SCLC, no brain mets	MRI Brain Surveillance alone MRI Brain Surveillance/PCI	OS

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ES SCLC – First-line therapy

Key 1st line ICI Studies in ES SCLC

Trial Name	IMpower 133	CASPIAN		CAPSTONE-1	KEYNOTE-604	ASTRUM-005
N	201 vs. 202	268 vs. 269 vs. 269		230 vs. 232	228 vs. 225	389 vs. 196
Treatment arms	Atezolizumab + EC vs. Placebo + EC	Durvalumab +EC/EP vs. EC/ EP	Durvalumab+ tremelimumab+ EC/EP vs. EC/EP	Adebrelimab+EC vs. placebo+EC	Pembrolizumab+EC/ EP vs. Placebo+EC/EP	Serplulimab+EC vs. placebo+EC
Median follow-up	13.9m	14.2m	25.1m	13.5m	21.6m	12.3m
OS (months; HR, 95% CI)	12.3 vs. 10.3 0.70 (0.54–0.91)	13.0 vs. 10.3 0.73 (0.59–0.91)	10.4 vs. 10.5 0.82 (0.68–1.00)	15.3 vs. 12.8 0.72 (0.58–0.90)	10.8 vs. 9.7 0.80(0.64–0.98)	15.4 vs. 10.9 0.63(0.49–0.82)
OS rate at 1 year	51.7% vs. 38.2%	54% vs. 40%	43.8% vs. 39.3%	62.9% vs. 52.0%	45.1% vs. 39.6%	60.7% vs. 47.8%
OS rate at 2 year	NA	NA	23.4% vs. 14.4%	31.3% vs. 17.2%	22.5% vs. 11.2%	43.1% vs. 7.9%
PFS, (months; HR, 95% CI)	5.2 vs. 4.3 0.77 (0.62–0.96)	5.1 vs. 5.4 0.78 (0.65–0.94)	4.9 vs. 5.4 0.84 (0.70–1.01)	5.8 vs. 5.6 0.67 (0.54–0.83)	4.5 vs. 4.3 0.75 (0.61–0.91)	5.7 vs. 4.3 0.48(0.38–0.59)
ORR	60.2% vs. 64.4%	68% vs. 58%	58% vs. 58%	70.4% vs. 65.9%	70.6% vs. 61.8%	80.2% vs. 70.4%

Modified from Zhang et al., Front Oncol 2023

CASPIAN: 3 year data

CASPIAN Study Design

Phase 3, global, randomized, open-label, active-controlled, multicenter study

- Treatment-naïve ES-SCLC
- WHO PS 0 or 1
- Asymptomatic or treated and stable brain metastases permitted
- Life expectancy ≥12 weeks
- Measurable disease per RECIST v1.1

N=805 (randomized)

1:1:1 (R) Stratified by planned platinum (carboplatin vs cisplatin)

Durvalumab + tremelimumab + EP* q3w for 4 cycles	Durvalumab‡ q4w until PD
Durvalumab + EP* q3w for 4 cycles	Durvalumab q4w until PD
EP* q3w for up to 6 cycles†	Optional PCI†

Primary endpoint
- OS

Secondary endpoints
- PFS§
- ORR§
- Safety & tolerability
- PROs

*EP consists of etoposide 80–100 mg/m2 with either carboplatin AUC 5–6 or cisplatin 75–80 mg/m2, durvalumab dosed at 1500 mg, tremelimumab dosed at 75 mg
†Patients could receive an additional 2 cycles of EP (up to 6 cycles total) and PCI at the investigator's discretion
‡Patients received an additional dose of tremelimumab post-EP; §By investigator assessment per RECIST v1.1
AUC, area under the curve; ORR, objective response rate; PCI, prophylactic cranial irradiation; PD, disease progression; PFS, progression-free survival; PROs, patient-reported outcomes; PS, performance status; q3w, every 3 weeks; q4w, every 4 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1

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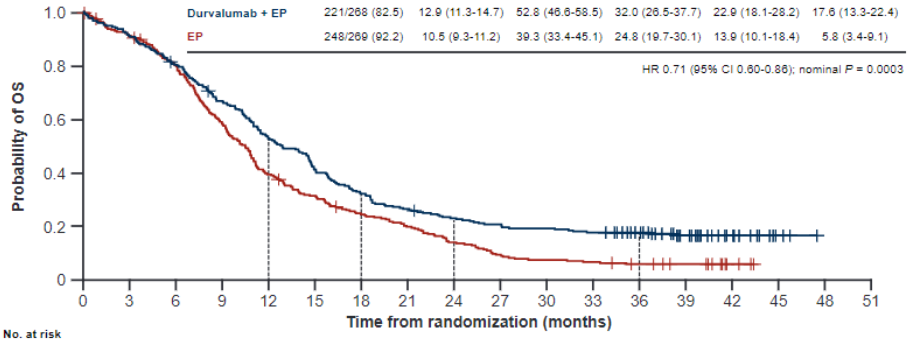
	Events/ patients, n (%)	Median OS (95% CI), months	12-month OS rate (95% CI), %	18-month OS rate (95% CI), %	24-month OS rate (95% CI), %	36-month OS rate (95% CI), %
Durvalumab + EP	221/268 (82.5)	12.9 (11.3-14.7)	52.8 (46.6-58.5)	32.0 (26.5-37.7)	22.9 (18.1-28.2)	17.6 (13.3-22.4)
EP	248/269 (92.2)	10.5 (9.3-11.2)	39.3 (33.4-45.1)	24.8 (19.7-30.1)	13.9 (10.1-18.4)	5.8 (3.4-9.1)

HR 0.71 (95% CI 0.60-0.86); nominal *P* = 0.0003



No. at risk

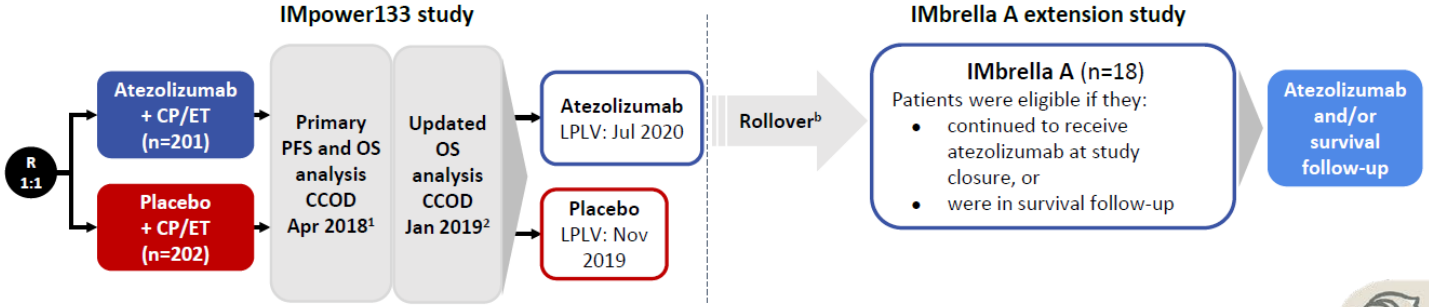
urvalumab + EP	268	244	214	177	140	109	85	70	60	54	50	46	39	25	13	3	0	0
EP	269	243	212	156	104	82	64	51	36	24	19	17		10	3	0	0	0

Three times more patients were estimated to be alive at 3 years (17.6 vs 5.8%)

IMbrella extension study

IMbrella A: an extension study of IMpower133[a]

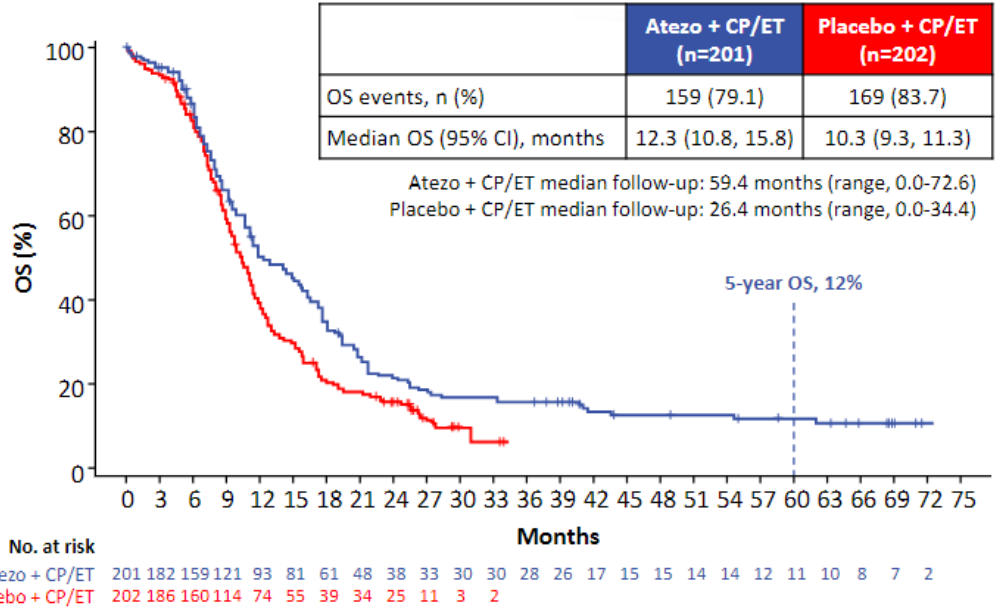
- IMbrella A is an open-label, non-randomised, multicentre extension and long-term observational study
- Patients in the IMpower133 control arm were not eligible for enrollment in IMbrella A
- Rollover from IMpower133 to IMbrella A for patients treated with atezolizumab in IMpower133 occurred between December 2019 and July 2020
- We report a merged analysis from IMpower133 and IMbrella A with a CCOD of 16 March 2023



Atezolizumab, 1200 mg IV, Day 1; CP, AUC 5 mg/mL/min IV, Day 1; ET, 100 mg/m² IV, Days 1–3. CCOD, clinical cutoff date; LPLV, last patient, last visit. [a] IMbrella A (NCT03148418) allowed rollover from other Roche/Genentech-sponsored atezolizumab trials; only results from patients who rolled over from IMpower133 are reported. [b] Eight patients who were alive did not rollover to IMbrella A (censored). 1. Horn L, et al. N Engl J Med 2018;379:2220-92; 2. Liu SV, et al. J Clin Oncol 2021; 39:619-30.

Liu et al., WCLC 2023 proceedings; https://ter.li/b12nvl

IMbrella long-term OS



	Atezo + CP/ET (n=201)	Placebo + CP/ET (n=202)
OS events, n (%)	159 (79.1)	169 (83.7)
Median OS (95% CI), months	12.3 (10.8, 15.8)	10.3 (9.3, 11.3)

Atezo + CP/ET median follow-up: 59.4 months (range, 0.0-72.6)
Placebo + CP/ET median follow-up: 26.4 months (range, 0.0-34.4)

OS rate (95% CI), %	IMpower133 and IMbrella A Atezo + CP/ET (n=201)	IMpower133 only Placebo + CP/ET (n=202)
1-year	52% (45-59)	39% (32-46)
2-year	22% (16-28)	16% (11-21)
3-year	16% (11-21)	NE[a]
4-year	13% (8-18)	NE[a]
5-year	12% (7-17)	NE[a]

Clinical cutoff date: 16 March 2023. NE, not estimable. [a] OS rates were NE in the control arm as rollover to IMbrella A was not permitted.

Liu et al., WCLC 2023 proceedings; https://ter.li/b12nvl

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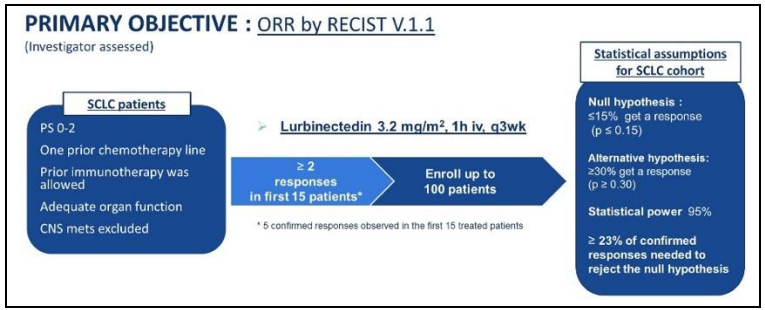
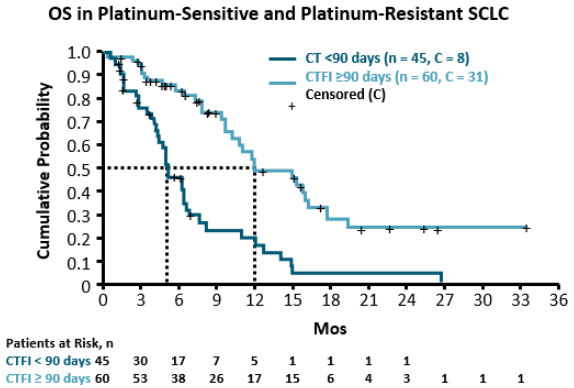
Relapsed SCLC

Lurbinectedin

Single arm Ph2 in relapsed SCLC





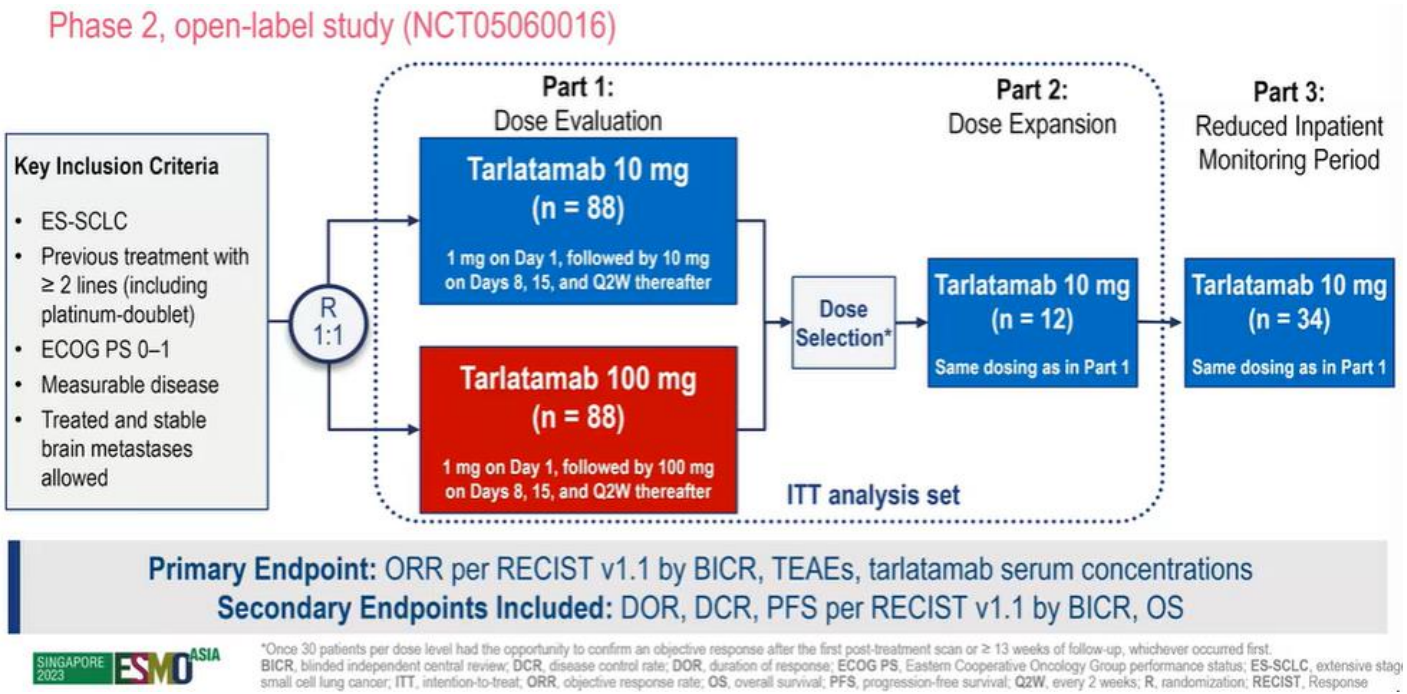
	Basket phase 2 study SCLC cohort Lurbinectedin (n = 83)		ATLANTIS phase 3 study Topotecan subgroup (n = 98)	
	IA	IRC	IA	IRC
ORR, % (95 % CI)	41.0 (30.3–52.3)	33.7 (23.7–44.9)	25.5 (17.2–35.3)	25.5 (17.2–35.3)
DoR (months), median (95 % CI)	5.3 (3.5–5.9)	5.1 (4.8–5.9)	3.9 (3.0–5.7)	4.3 (3.0–5.6)
PFS (months), median (95 % CI)	4.0 (2.6–4.7)	3.7 (2.6–4.6)	4.2 (3.0–4.8)	4.1 (2.9–4.7)
OS (months), median (95 % CI)	10.2 (7.6–12.0)		7.6 (6.1–10.3)	
% events	74 (89.2 %)		80 (81.6 %)	
Censored	9 (10.8 %)		18 (18.4 %)	

Abbreviations: CI, confidence interval; DoR, duration of response; IA, investigator assessment; IRC, Independent Review Committee; ORR, overall response rate; PFS, progression free survival; OS, overall survival.

- June 2020, lurbinectedin received accelerated FDA approval for relapsed SCLC → now approved in 16 territories
- Full approval will require confirmation by the Phase 3 LAGOON Study which compared lurbinectedin to irinotecan (or investigator's choice)

Trigo. Lancet Oncol. 2020;21:645; Peters S, Lung Cancer 2024

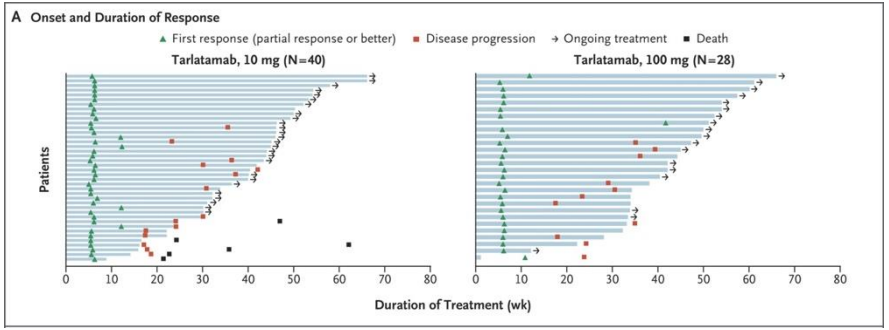
DeLLphi-301: Tarlatamab in relapsed SCLC



Paz Ares et al, EMSO Asia 2023, Ahn NEJM 2023 DOI: 10.1056/NEJMoa2307980

Tarlatamab DeLLphi -301 responses

Variable	Tarlatamab, 10 mg (N=100)	Tarlatamab, 100 mg (N=88)
Best overall response — no. (%)		
Objective response		
Confirmed complete response	1 (1)	7 (8)
Confirmed partial response	39 (39)	21 (24)
Stable disease	30 (30)	27 (31)
Progressive disease	20 (20)	13 (15)
Not evaluable†	2 (2)	4 (5)
Death before postbaseline scan†	6 (6)	13 (15)
No postbaseline scan†	2 (2)	3 (3)
Percentage of patients with objective response (97.5% CI)	40 (29–52)	32 (21–44)
Median duration of objective response (95% CI) — mo		
Overall	NE (5.9–NE)	NE (6.6–NE)
25th percentile	4.4 (2.8–7.1)	5.6 (2.8–7.6)
75th percentile	NE (NE–NE)	NE (NE–NE)
Observed duration of objective response — no./total no. (%)		
≥3 mo	35/40 (88)	25/28 (89)
≥6 mo	23/40 (58)	17/28 (61)
≥9 mo	10/40 (25)	10/28 (36)



Ahn NEJM 2023 DOI: 10.1056/NEJMoa2307980

Tarlatamab: Toxicities

Adverse Events	Tarlatamab, 10 mg		Tarlatamab, 100 mg
	Parts 1 and 2 (N=99)	Part 3, Reduced Monitoring (N=34)	Part 1 (N=87)
	number of patients (percent)		
Events during treatment period			
According to severity			
Any grade	96 (97)	34 (100)	87 (100)
Grade ≥2	86 (87)	33 (97)	83 (95)
Grade ≥3	57 (58)	22 (65)	56 (64)
Grade ≥4	16 (16)	7 (21)	13 (15)
Fatal	3 (3)	4 (12)	5 (6)
Serious adverse event	58 (59)	14 (41)	62 (71)
Event leading to dose interruption, dose reduction, or both	31 (31)	5 (15)	39 (45)
Event leading to tarlatamab discontinuation	7 (7)	3 (9)	6 (7)
Events of interest during treatment period			
Cytokine-release syndrome†			
Overall	49 (49)	19 (56)	53 (61)
Grade ≥3 severity	0	1 (3)	5 (6)
Serious	26 (26)	5 (15)	32 (37)
Leading to tarlatamab discontinuation	0	0	1 (1)
Fatal	0	0	0
ICANS and associated neurologic events‡			
Overall	7 (7)	4 (12)	24 (28)
Grade ≥3 severity	0	0	4 (5)
Serious	2 (2)	2 (6)	11 (13)
Leading to tarlatamab discontinuation	1 (1)	0	1 (1)
Fatal	0	0	0
Neutropenia			
Overall	18 (18)	5 (15)	14 (16)
Grade ≥3 severity	6 (6)	2 (6)	9 (10)
Serious	2 (2)	0	3 (3)
Leading to tarlatamab discontinuation	0	0	0
Fatal	0	0	0

Ahn NEJM 2023 DOI: 10.1056/NEJMoa2307980

FDA-approved agents for relapsed disease

Study	N	ORR (%)	mDOR (mo)	mPFS (mo)	mOS (mo)	Est survival at 6mo
Topotecan (1997)	101	21.7	7.6	2.8	5.4	
Lurbinectedin	105	35.2	5.3	3.5	9.3	67.1%
Tarlatamab (10mg)	100 34	40%	> 6 mo (in 59%)	4.9	68% at 9mo	73%

Ardizzoni et al, JCO 1997; Trigo et al., Peters. et al, Lung Cancer J 2024; Ahn MJ et al., NEJM 2023

ES SCLC – Select Ph3 or RPh2 First-line studies, reported

Study	Phase	Clinical Setting	Treatment arms	1º Endpoint(s)	Results/notes
SKYSCRAPER-2 NCT03043872	III	ES SCLC therapy naive	CE + atezo/pbo vs CE + atezo plus **tiragolumab**	IA OS IA PFS	Negative study
KEYVIBE-008 NCT05224141	III	ES SCLC therapy naive	CE + pembro/pbo vs CE + pembro plus **vibostolimab**	OS	Discontinue due to futility
SWOG1929 NCT04334941	RPII	Maintenance after chemoIO in SLFN11 (+) SCLC	Atezo vs Atezo + **Talazoparib**	PFS	Met primary endpoint of improved PFS Biomarker-based study
Anti-FucGM1 NCT05091567	RPII	ES SCLC therapy naive	CE + nivo vs CE + nivo + **BMS-986012**	Safety, PFS	Interim Analysis – dn demonstrate PFS improvement

Rudin et al. JCO 2024 DOI: https://doi.org/10.1200/JCO.23.01363; Press release @ https://www.merck.com/news; Karim et al., JTO 2024 doi: 10.1016/j.jtho.2024.10.021; Kalinka et al., 2024, Ann Oncol 2024;35(suppl):Abstr 1786O ESMO proceedings,

ES SCLC – Select Ph3 or RPh2 First-line studies, ongoing

Study	Phase	Clinical Setting	Treatment arms	1º EP	Notes
CASPIAN NCT05091567	III	ES SCLC therapy naive	Pbo/Pbo vs Durva + Treme	OS/PFS	Pending
IMforte NCT05091567	III	Post-EP atezo with at least SD	Atezo vs Atezo + **lurbinectedin**	OS/PFS	Press release - Statisically significant improvement in OS/PFS
DeLLphi-305 NCT 06211036	III	Post-EP IO with at least SD	Durva vs Durva + **Tarlatamab**	OS	Tarlatamab 10mg dose
S2409-PRISM (pending)	*RP2*	*Post-EP IO with at least SD*	*Durva vs* *Durva **+ targeted agents***	*PFS*	*Randomization based on SCLC subtype (ANPI) and SLFN11 status*
RADIATION					
RAPTOR (NRG-LU007; NCT 04402788)	RP2/3	At least SD after chemoIO and up to 3 visible liver metastases	Atezo vs Atezo + SBRT	IA PFS	Stratified by number of visible metastases

https://investor.jazzpharma.com/news-releases/news-release-details/jazz-pharmaceuticals-announces-statistically-significant-overall;

Summary

- 2024 was an exciting year for SCLC
- Durvalumab consolidation is the new SOC for LS SCLC after chemoRT
- Tarlatamab for relapsed SCLC, now FDA-approved
- To come – multiple active agents in evaluation in the relapsed setting
  - More BiTEs, and TRiTEs
  - Several active ADCs
  - Targeted therapies
  - Correlative science and biomarker-based studies