


The Future of Small Cell Lung Cancer Treatment: Potential Agents & Where Are We Going?

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INDIANA UNIVERSITY
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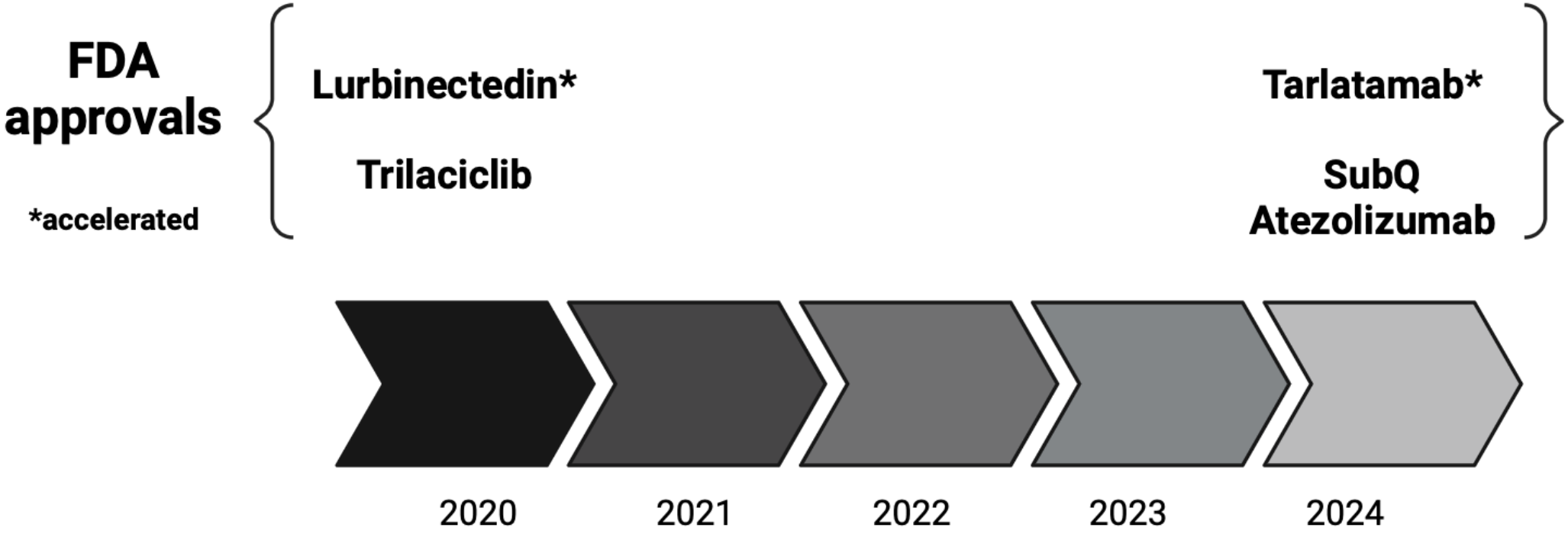
SCLC Treatment History: 2020 and beyond



** Durvalumab for limited-stage SCLC with breakthrough designation & under FDA priority review (Aug 2024)

Consolidation Durvalumab Post-CCRT Improves OS

ADRIATIC study design

Phase 3, randomized, double-blind, placebo-controlled, multicenter, international study (NCT03703297)

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

N=730

R‡

Durvalumab
1500 mg Q4W
N=264

Placebo
Q4W
N=266

Durvalumab + tremelimumab
D 1500 mg Q4W + T 75 mg Q4W for 4 doses, followed by D 1500 mg Q4W
N=200

cCRT components
- Four cycles of platinum and etoposide (three permitted†)
- RT: 60–66 Gy QD over 6 weeks or 45 Gy BID over 3 weeks
- RT must commence no later than end of cycle 2 of CT

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

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

Dual primary endpoints:
- Durvalumab vs placebo
  - OS
  - PFS (by BICR, per RECIST v1.1)

Key secondary endpoints:
- Durvalumab + tremelimumab vs placebo
  - OS
  - PFS (by BICR, per RECIST v1.1)

Other secondary endpoints:
- OS/PFS landmarks
- Safety

*cCRT and PCI treatment, if received per local standard of care, must have been completed within 1–42 days prior to randomization.
†If disease control was achieved and no additional benefit was expected with an additional cycle of chemotherapy, in the opinion of the investigator.
‡The first 600 patients were randomized in a 1:1:1 ratio to the 3 treatment arms; subsequent patients were randomized 1:1 to either durvalumab or placebo.

BICR, blinded independent central review; BID, twice daily; CT, chemotherapy; D, durvalumab; PCI, prophylactic cranial irradiation; PS, performance status; Q4W, every 4 weeks; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; RT, radiotherapy; T, tremelimumab; WHO, World Health Organization.

2024 ASCO ANNUAL MEETING #ASCO24 PRESENTED BY: Dr David R. Spigel

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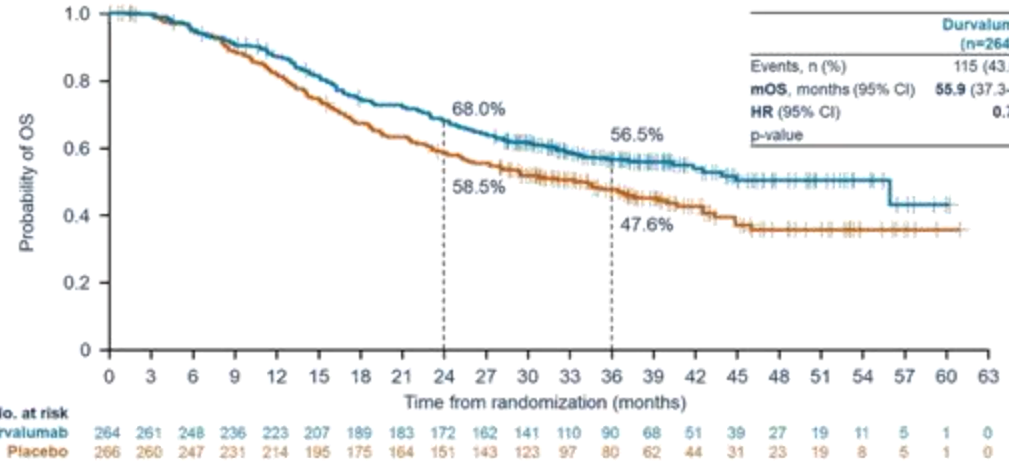
ASCO KNOWLEDGE CONQUERS CANCER

Overall survival (dual primary endpoint)

- Median duration of follow up in censored patients: 37.2 months (range 0.1–60.9)



	Durvalumab (n=264)	Placebo (n=266)
Events, n (%)	115 (43.6)	146 (54.9)
mOS, months (95% CI)	**55.9** (37.3–NE)	**33.4** (25.5–39.9)
HR (95% CI)	**0.73** (0.57–0.93)	
p-value	0.0104	

No. at risk																						
Durvalumab	264	261	248	236	223	207	189	183	172	162	141	110	90	68	51	39	27	19	11	5	1	0
Placebo	266	260	247	231	214	195	175	164	151	143	123	97	80	62	44	31	23	19	8	5	1	0

OS was analyzed using a stratified log-rank test adjusted for receipt of PCI (yes vs no). The significance level for testing OS at this interim analysis was 0.01679 (2-sided) at the overall 4.5% level, allowing for strong alpha control across interim and final analysis timepoints.

CI, confidence interval; mOS, median OS; NE, not estimable.

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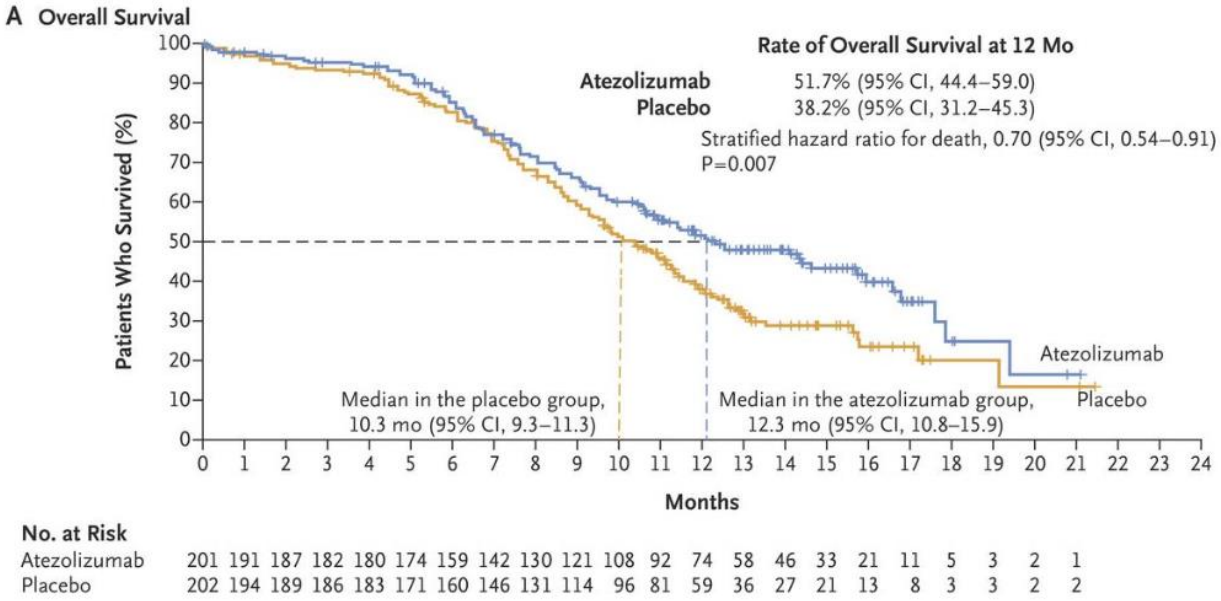
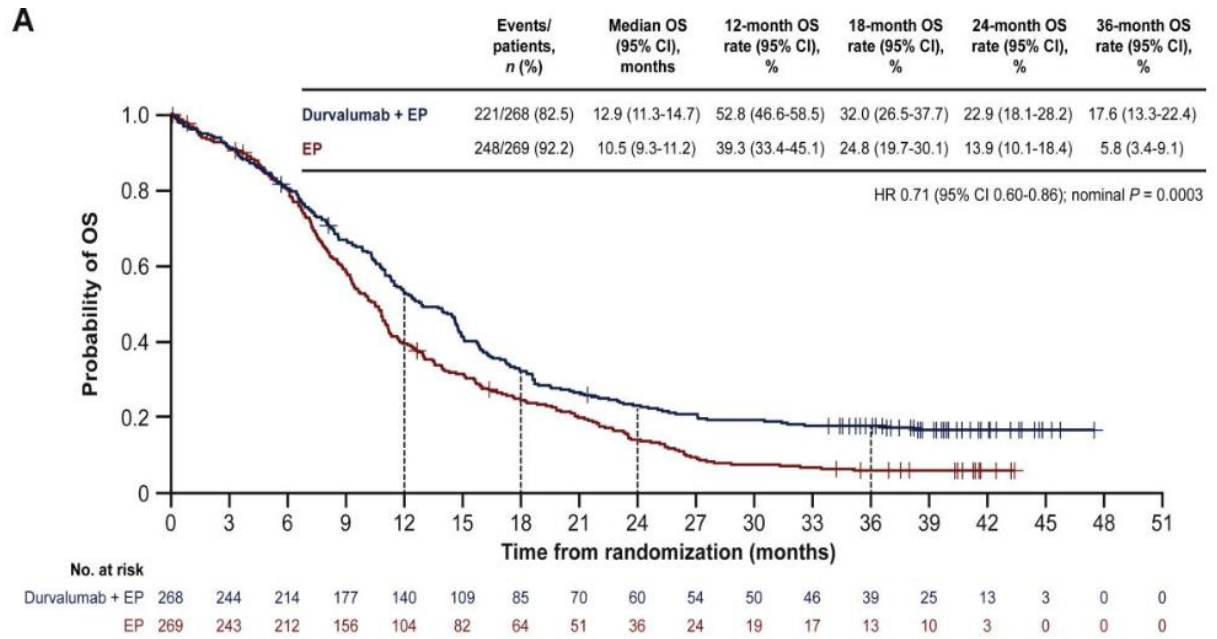
Chemoimmunotherapy in ES-SCLC



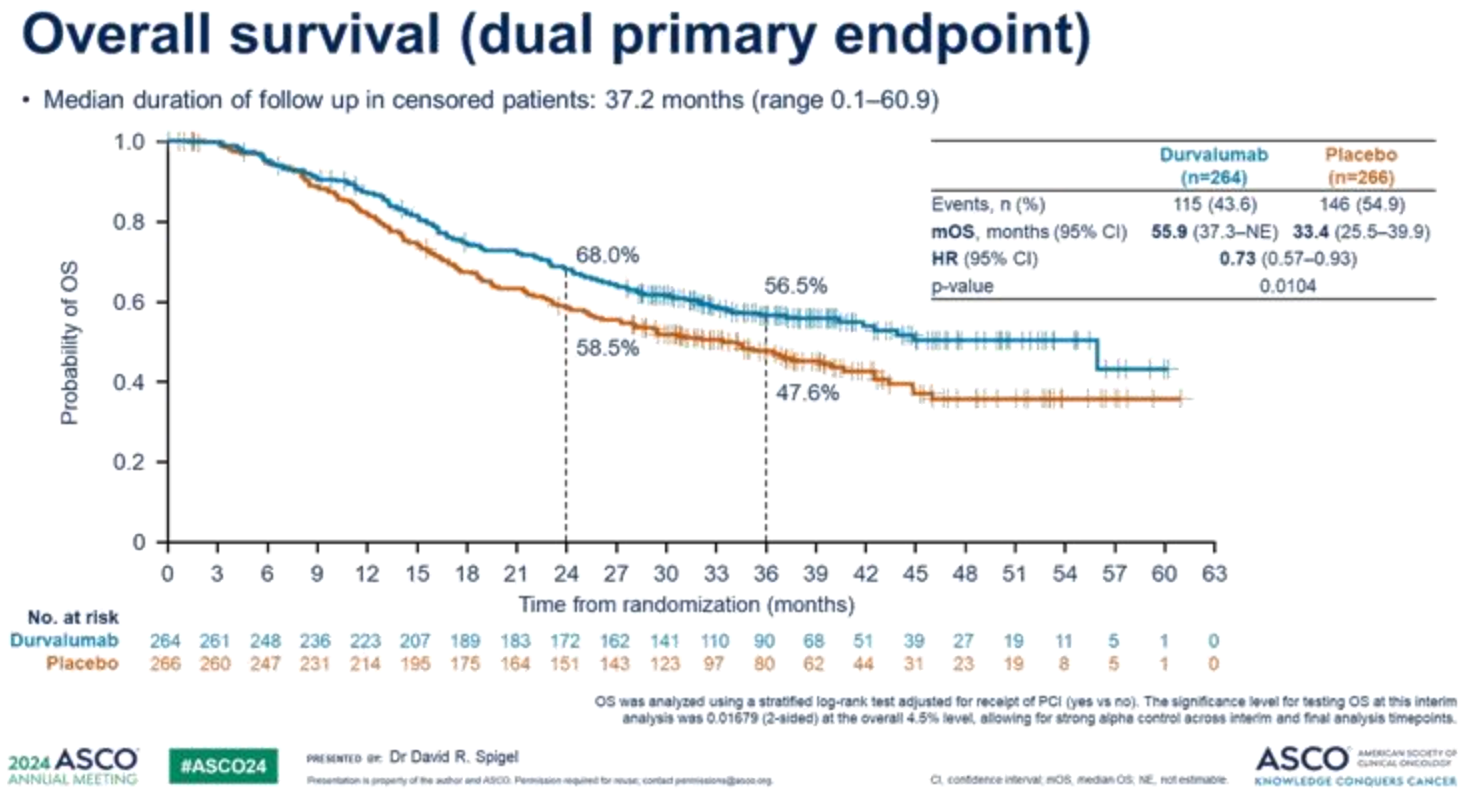
IMpower133



CASPIAN

Horn, et al. *NEJM* 2018; Paz-Ares, et al. *Lancet* 2019/ESMO Open 2022.

Why does IO impact LS-SCLC more than ES-SCLC?



Unmet Translational Need for SCLC – What Drives This Response?

Abscopal effect? Upregulation of MHC Class I? Increase in neoantigens? Particular NE subtype?

Treatment of Relapsed/Recurrent ES-SCLC

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2025
Small Cell Lung Cancer

NCCN Guidelines Index
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Discussion

SCLC SUBSEQUENT SYSTEMIC THERAPY (PS 0–2)[g] Consider dose reduction or growth factor support for patients with PS 2
CHEMOTHERAPY-FREE INTERVAL (CTFI) >6 MONTHS
Preferred Regimens • Clinical trial enrollment • Re-treatment with platinum-based doublet[h,15-19] **Other Recommended Regimens** • Lurbinectedin[20,21] • Topotecan oral (PO) or intravenous (IV)[22-25] • Irinotecan[i,25,26] • Tarlatamab-dlle[i,28]
CTFI ≤6 MONTHS
Preferred Regimens • Clinical trial enrollment • Lurbinectedin[20,21] • Topotecan oral (PO) or intravenous (IV)[17,22-25] • Irinotecan[i,25,26] • Tarlatamab-dlle[j,28] • Re-treatment with platinum-based doublet may be considered for CTFI 3–6 months[h,17-19] **Other Recommended Regimens** • Nivolumab or pembrolizumab (if not previously treated with an ICI)[d,29-33] • Paclitaxel[34,35] • Temozolomide[36,37] • Cyclophosphamide/doxorubicin/vincristine (CAV)[22] • Docetaxel[38] • Gemcitabine[27,39,40] • Oral etoposide[41,42]

Lurbinectedin

Selective inhibitor of transcription & TME

Phase 2 single-arm basket trial

105 pts with relapsed SCLC (2 or 3L)

3.2 mg/m^2 dose IV q3weeks

1° endpoint: Overall response rate = **35.2%**

Platinum-response: **45.0%** (S) vs **22.2%** (R)

Phase 3 LAGOON in SCLC (ongoing)

Accelerated FDA approval (June 2020)

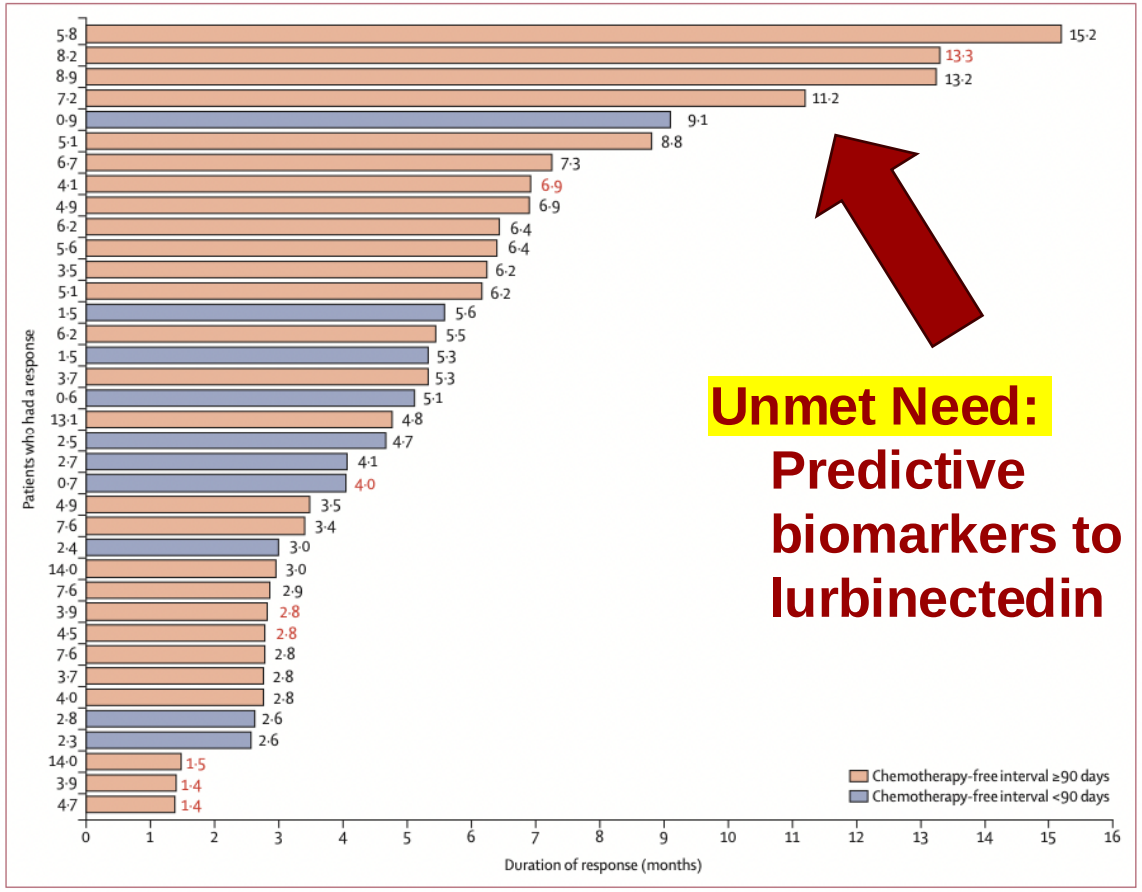
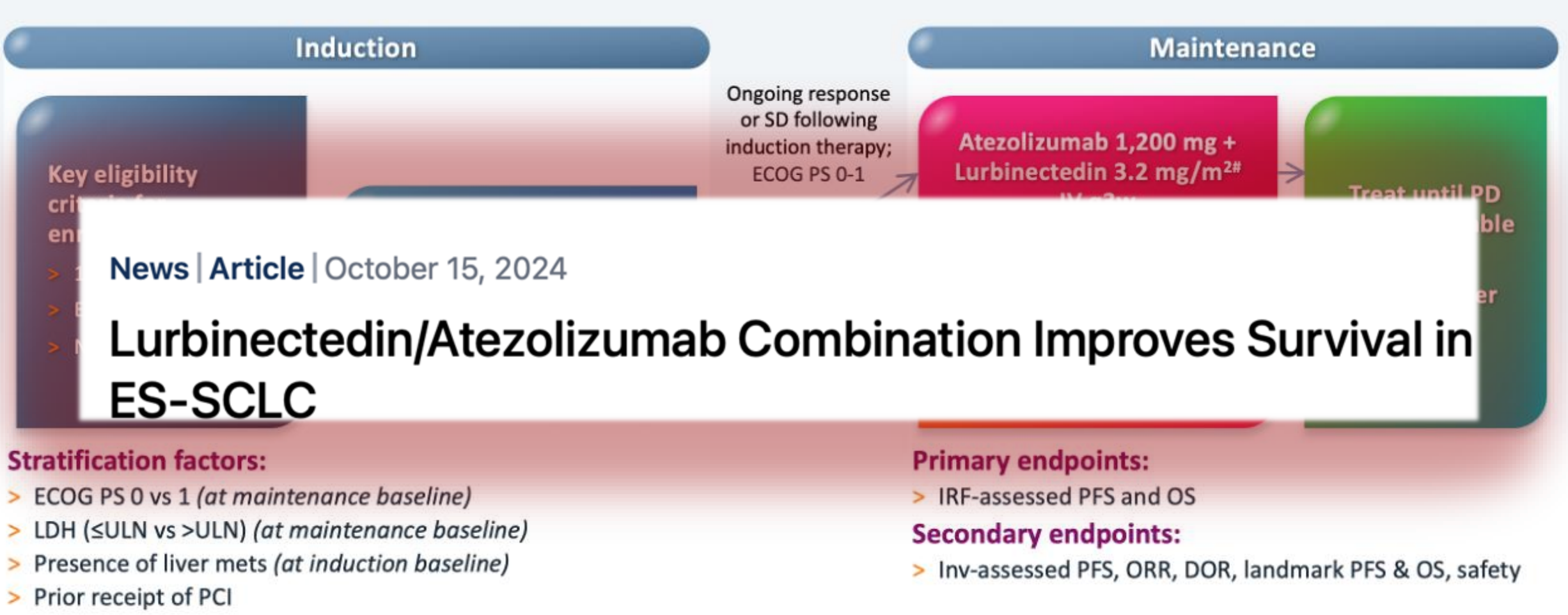


Figure 1: **Duration of response by investigator assessment**
Each bar represents a patient with SCLC who responded to treatment (n=37). Data shown on the left of each bar are the chemotherapy-free interval (months); data shown on the right of each bar are the duration of response (0 is the time of starting response). Data in red font refer to eight patients censored at the cutoff date: seven with no documented progression (under follow-up) and one who discontinued treatment due to an investigator's decision and then received further therapy. SCLC=small-cell lung cancer.

Trigo, et al. *Lancet Oncol.* 2020.

IMforte: Addition of Lurbinectedin to Atezolizumab Maintenance



Tarlatamab

Bispecific T-cell Engager (BiTE): DLL3, CD3

Phase 2 DeLLphi-301 (NCT05060016)

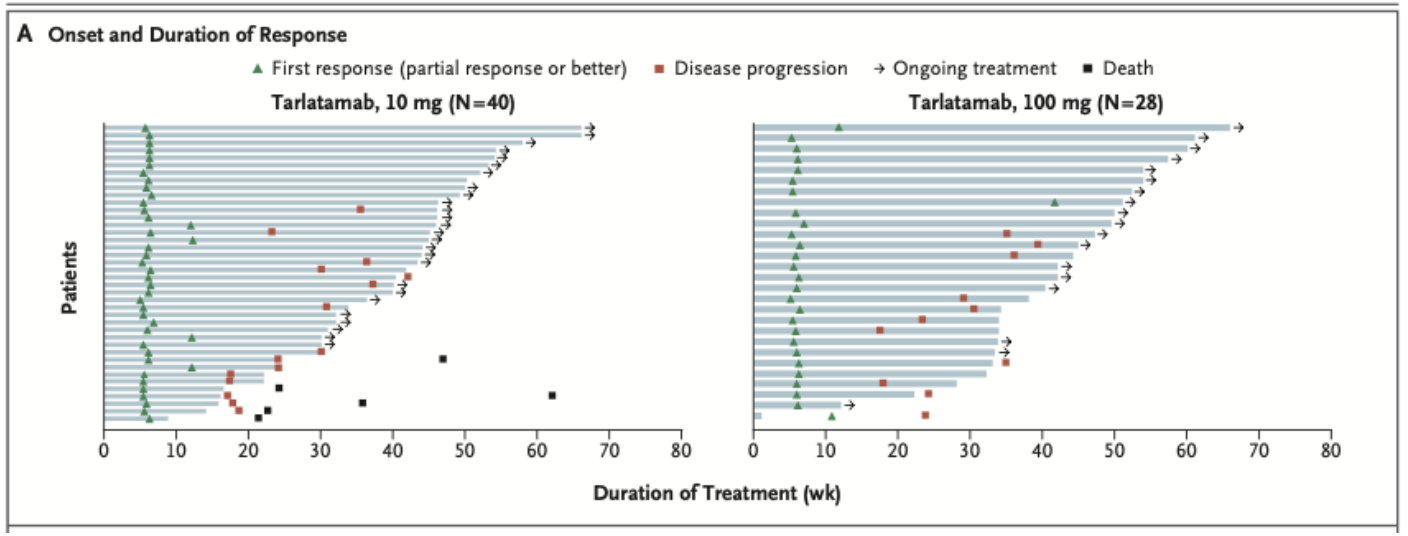
220 pts: 10 mg or 100 mg cohorts q2w

ORR: 40% (10 mg), 32% (100 mg)

mDOR: >6 months in 59% pts

TRAE: Low-grade CRS, neurotoxicity

C1D1 & C1D8 require 22-24h observation



Responses to tarlatamab are durable

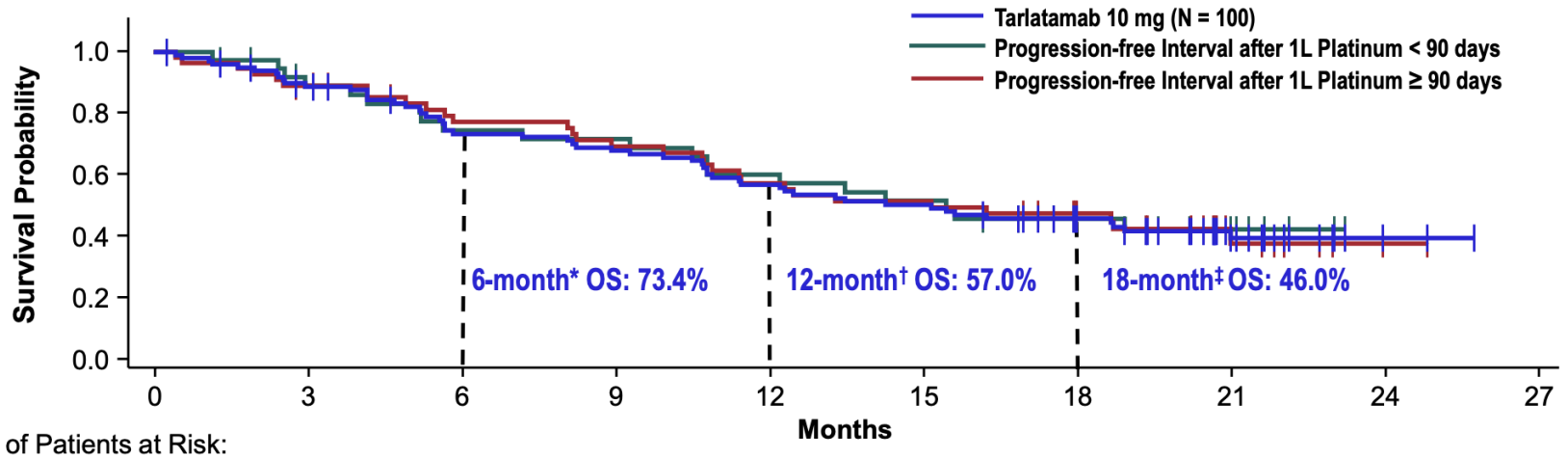
Accelerated FDA approval (May 16, 2024)

Ahn, et al. *NEJM*. 2023.

Tarlatamab Improves OS Regardless of Platinum-Response/CTFI

DeLLphi 301

Overall Survival



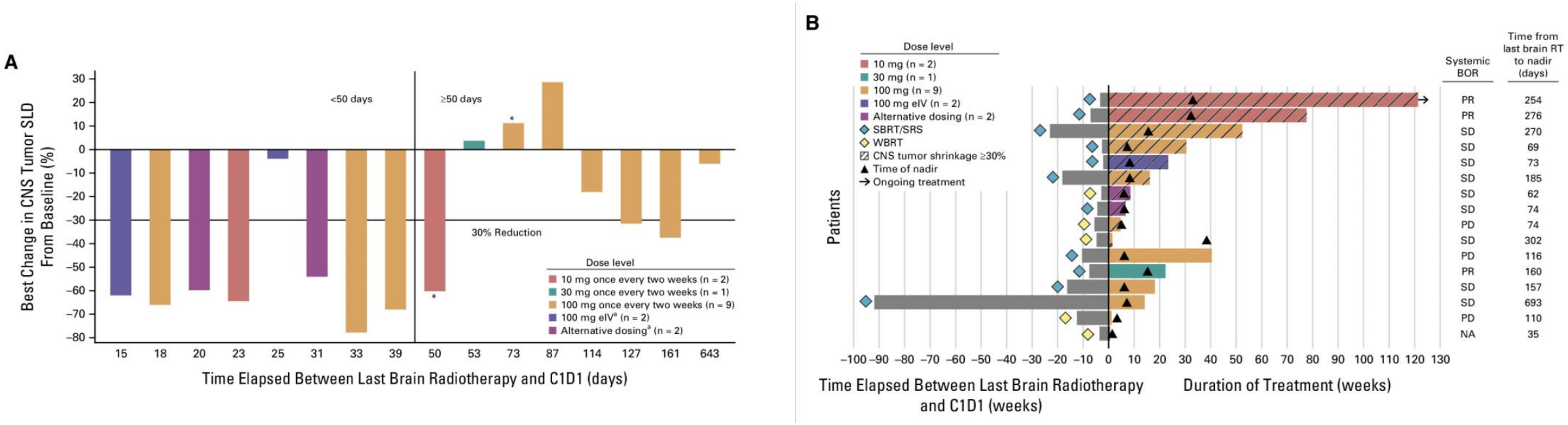
Number of Patients at Risk:

Tarlatamab 10 mg	100	84	67	62	52	46	36	18	3	0
< 90 days	39	31	26	25	21	18	13	7	0	
≥ 90 days	55	48	39	35	29	26	21	9	2	0

OS was similar regardless of progression-free interval after 1L platinum treatment (< 90 d vs ≥ 90 d)

Median follow-up for OS was 20.7 months. Data cutoff, May 16, 2024. The efficacy analysis set consists of patients in Parts 1 and 2 (N = 100). One patient did not receive tarlatamab 10 mg but was included in ITT analysis. Part 3 was a safety substudy and was not included in this response analysis. *95% CI, 63.2–81.2. †95% CI, 46.3–66.3. ‡95% CI, 35.6–55.8. Progression-free interval after first line platinum treatment is defined as days from the last first line platinum treatment to disease progression or start of second line treatment, whichever is earlier. **ITT,** intention-to-treat; **NE**, not estimable; **OS**, overall survival.

Tarlatamab Harbors Intracranial Efficacy

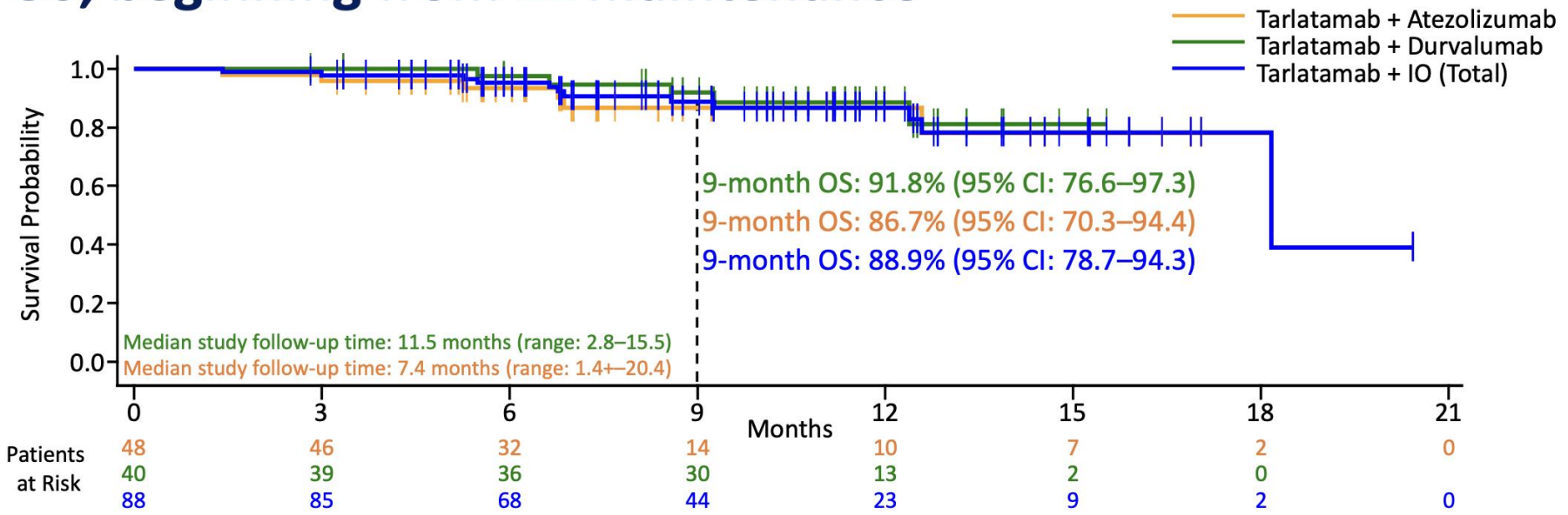


Concordance seen between systemic disease control and >30% brain metastasis shrinkage; 87.5% intracranial disease control rate (14 of 16 pts).

Dowlati, et al. *JCO*. 2024.

Tarlatamab Addition to 1L ChemoIO Maintenance

OS, beginning from 1L maintenance



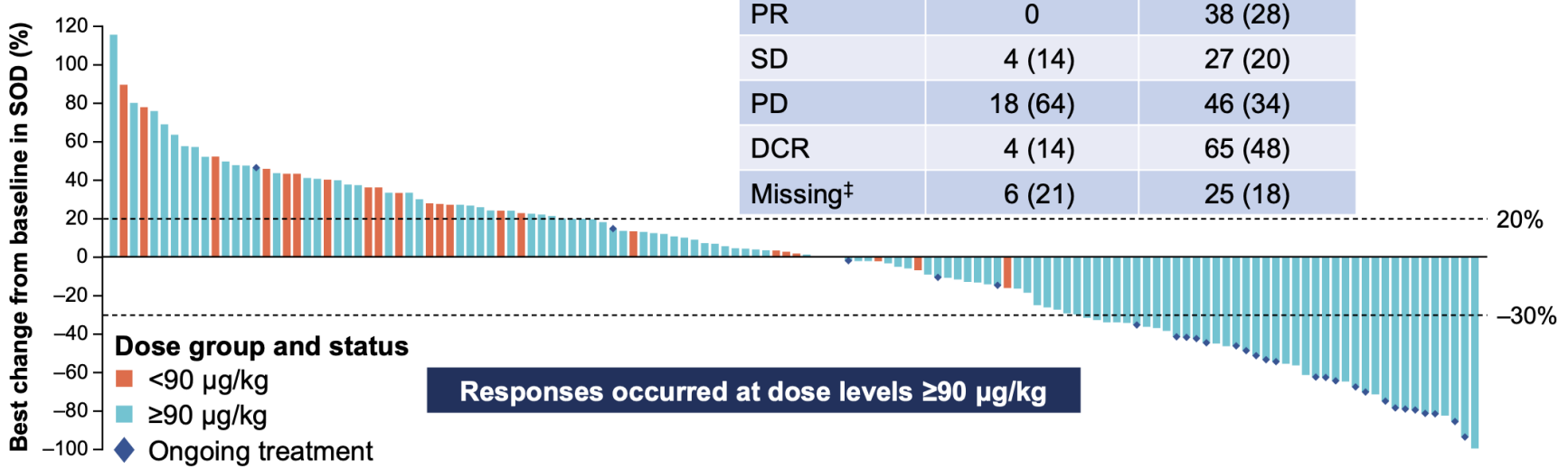
After a median time from 1L chemoimmunotherapy to 1LM of 3.6 months, tarlatamab with a PD-L1 inhibitor as 1LM showed a 9-month OS of 89%.

+ , censored; **1L,** first-line; **1LM,** first-line maintenance; **CI,** confidence interval; **IO,** immuno-oncology agent; **OS,** overall survival; **PD-L1**, programmed death-ligand 1.

BI 764532/Obrixtamig: DLL3 BiTE in ES-SCLC/LCNEC/EPNEC

Efficacy in all patients

Response n, (%)*	All patients (<90 µg/kg) n=28†	All patients (≥90 µg/kg) n=136†
PR	0	38 (28)
SD	4 (14)	27 (20)
PD	18 (64)	46 (34)
DCR	4 (14)	65 (48)
Missing‡	6 (21)	25 (18)



*Best overall response is reported regardless of confirmation; †Efficacy population: started treatment ≥7 weeks prior to data cut-off (responses evaluated per RECIST v1.1 criteria); ‡Assessable patients who did not have any tumor assessment due to early toxicity, start of subsequent anti-cancer therapy, death or any other reason

Data cut-off: Feb 21, 2024
DCR, disease control rate; PD, progressive disease; PR, partial response; RECIST v.1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease; SOD, sum of diameters

Where Are We Going with DLL3 BiTEs: New Studies

- DeLLphi-305 - Tarlatamab + Durvalumab vs Durvalumab alone following ChemoIO in ES-SCLC

  Phase 3 NCT06211036 Estimated Completion ~9/2028
- DeLLphi-306 - Tarlatamab vs Placebo post CCRT in LS-SCLC

  Phase 3 NCT06117774 ~10/2029
- DeLLphi-308 - Subcutaneous Tarlamatab in ES-SCLC

  Phase 1 NCT06598306 ~5/2028

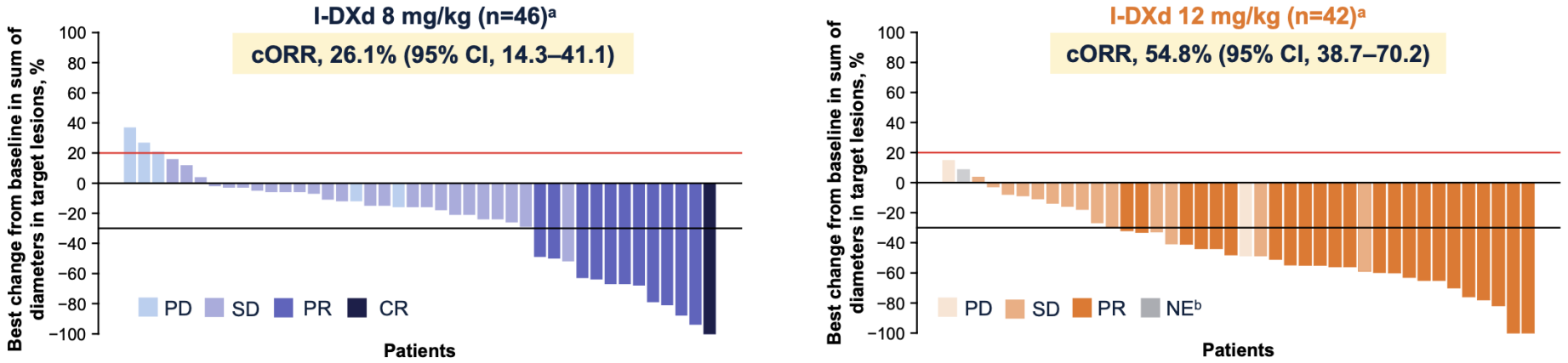
- DAREON-8 – BI 764532 + ChemoIO in ES-SCLC

  Phase 1 NCT06077500 ~6/2026
- DAREON-9 – BI 764532 + Single Agent Chemo (Topotecan or Lurbinectedin) for Relapse ES-SCLC

  Phase 1 NCT05990738 ~4/2026

Ifinatamab Deruxtecan (I-DXd) in ES-SCLC

I-DXd has promising antitumor activity; patients treated with 12 mg/kg had a higher ORR than those treated with 8 mg/kg



Confirmed response by BICR[c]	I-DXd 8 mg/kg n=46	I-DXd 12 mg/kg n=42
ORR, % (95% CI)	26.1 (14.3–41.1)	54.8 (38.7–70.2)
CR, n (%)	1 (2.2)	0
PR, n (%)	11 (23.9)	23 (54.8)
DCR, % (95% CI)	80.4 (66.1–90.6)	90.5 (77.4–97.3)

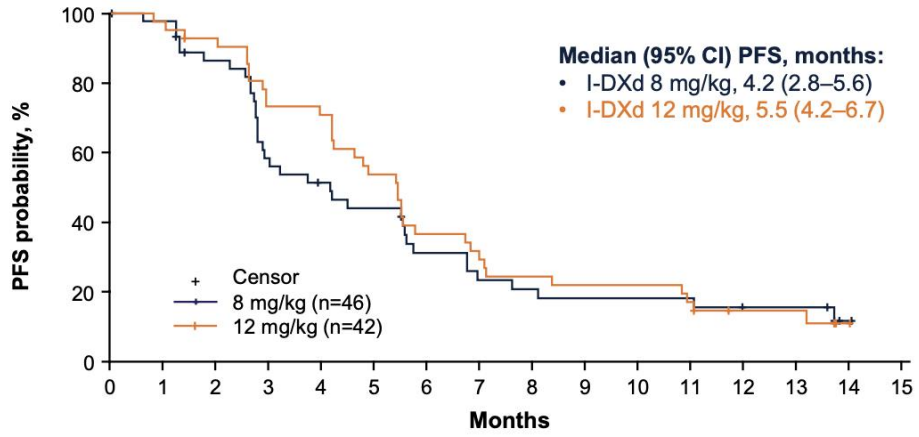
Data cutoff: April 25, 2024. The median follow-up for 8-mg/kg and 12-mg/kg cohorts was 14.6 months (range, 0.6–17.0) and 15.3 months (range, 0.8–20.3) respectively.

[a]Only patients with measurable disease at baseline and ≥1 post-baseline tumor scan were included in the waterfall plot: in the I-DXd 8-mg/kg cohort, n=42; 2 patients died and 2 patients withdrew consent before the Week 6 assessment; in the 12-mg/kg cohort, n=40; 1 patient died before the Week 6 assessment and 1 patient did not have target lesions at baseline. [b]This patient has a BOR of NE because the only post-baseline tumor scan was conducted outside the designated time window; the timepoint response was SD. [c]Per RECIST 1.1.

BICR, blinded independent central review; BOR, best overall response; cORR, confirmed ORR; CR, complete response; DCR, disease control rate; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; SD, stable disease.

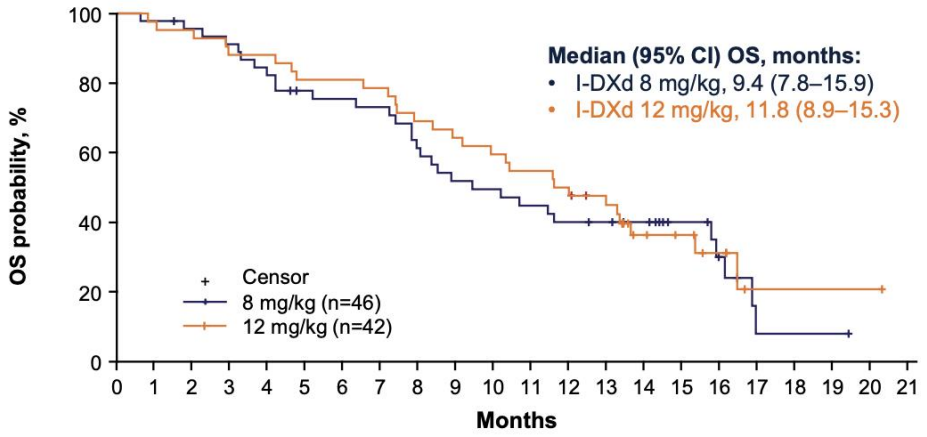
Ifinatamab Deruxtecan (I-DXd) in ES-SCLC

PFS and OS were similar between study arms, numerically favoring the I-DXd 12-mg/kg dose



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

Data cutoff: April 25, 2024. The median follow-up for 8-mg/kg and 12-mg/kg cohorts was 14.6 months (range, 0.6–17.0) and 15.3 months (range, 0.8–20.3) respectively.
OS, overall survival; PFS, progression-free survival.

Ifinatamab Deruxtecan (I-DXd) in ES-SCLC

Efficacy summary in patients with brain metastases at baseline and in a subset of patients with brain target lesions at baseline

	Patients with brain metastases at baseline		Patients with brain target lesions at baseline			
	Systemic response[a]		Systemic response[a]		Intracranial response[b]	
	I-DXd 8 mg/kg n=19	I-DXd 12 mg/kg n=18	I-DXd 8 mg/kg n=6	I-DXd 12 mg/kg n=10	I-DXd 8 mg/kg n=6	I-DXd 12 mg/kg n=10
Confirmed ORR,[a] % (95% CI)	26.3 (9.1–51.2)	61.1 (35.7–82.7)	16.7 (0.4–64.1)	60.0 (26.2–87.8)	66.7 (22.3–95.7)	50.0 (18.7–81.3)
Best overall response,[a] n (%)						
CR	1 (5.3)	0	1 (16.7)	0	2 (33.3)	2 (20.0)
PR	4 (21.1)	11 (61.1)	0	6 (60.0)	2 (33.3)	3 (30.0)
SD	11 (57.9)	5 (27.8)	3 (50.0)	3 (30.0)	2 (33.3)	5 (50.0)
PD	2 (10.5)	2 (11.1)	2 (33.3)	1 (10.0)	0	0
NE	1 (5.3)	0	0	0	0	0

I-DXd has effective intracranial activity

Antibody Drug Conjugates in ES-SCLC

ADC	Target	Payload Target
ABBV-706	SEZ6	Topoisomerase 1
ABBV-011	SEZ6	Calicheamicin
Ifinatamab deruxtecan	**B7H3**	**Topoisomerase 1**
Sacituzumab govitecan	Trop2	Topoisomerase 1
Rovalpituzumab tesirine	DLL3	Pyrrolobenzodiazepine

WHAT OTHER SURFACE TARGETS SHOULD BE ADDRESSED?

WHAT ABOUT ADCs with DUAL PAYLOADS?

Where Are We Going: Ongoing Trials in SCLC

- **ASTRIDE** Phase 3 *Serplulimab + EP vs Atezolizumab + EP in ES-SCLC* - NCT05468489 ~12/2025
- **LAGOON** Phase 3 *Lurbinectedin Alone vs with Irinotecan vs Investigators Choice* - NCT05153239 ~4/2026
- **IDeate-Lung03** Phase 1/2 IDXd in 1) Maintenance and in 2) Induction for ES-SCLC - NCT06362252 ~12/2026
- **Serplulimab** (anti-PD1) with CCRT followed by 1Y Maintenance in LS-SCLC Phase 3 - NCT05353257 ~12/2026
- **RAPTOR** Phase 2/3 *Thoracic Radiotherapy to IO Maintenance for ES-SCLC* - NCT04402788 ~4/2027
- **MAVERICK** (S1827) Phase 3 *MRI q3m vs PCI in LS- and ES-SCLC* - NCT04155034 ~11/2027
- **IDeate-Lung02** Phase 3 *IDXd vs Investigators Choice for Relapsed ES-SCLC* - NCT06203210 ~2/2029
- **Toripalimab** (anti-PD1) or in Combo With Tifcemalimab (JS004/TAB004, anti-BTLA) after CCRT in LS-SCLC Phase 3 - NCT06095583 ~7/2029

S2409 - PRISM

S2409-PRISM: A Multicohort **PR**ec**I**sion **S**CLC Subtype **M**aintenance Phase II Trial of Immunotherapy Versus Biomarker-Directed Novel Agents in Combination with Immunotherapy in Extensive Stage Small Cell Lung Cancer (ES-SCLC)

Step 1: Tissue screening & Induction (n=~900)

- ES-SCLC Screening
- Tissue available for testing
- Asymptomatic or Stable Treated Brain Lesions
- Allows consent after initial cycle for tissue screening

Step 2: Randomization (n=312)

Subtypes A/N, SLFN11 pos or Subtype P N=134	Immunotherapy + PARP inhibitor / Immunotherapy
Subtypes A/N, SLFN11 neg N=84	Immunotherapy + ATR inhibitor / Immunotherapy
Subtype I N=84	Immunotherapy + NK activator / Immunotherapy

Primary Endpoints: PFS

Secondary Endpoints: OS, Frequency, Severity of Adverse Events

SWOG CANCER RESEARCH NETWORK

NCI National Clinical Trials Network — a National Cancer Institute program

NCI Community Oncology Research Program — A program of the National Cancer Institute of the National Institutes of Health

Courtesy of Dr. Anne Chiang

Final Thoughts

- Immunotherapy with Durvalumab is now SOC post CCRT for LS-SCLC
- Can IO Be IMPROVED with LS-SCLC post CCRT? Does Dual IO = BETTER Outcomes?
- Do We NEED PCI in LS-SCLC ANYMORE?
- Awaiting Data for IMforte - Lurbinectedin + Atezolizumab for ES-SCLC Maintenance Therapy
- DLL3 BiTEs – Moving Earlier in Treatment Landscape (Maintenance ES-SCLC, Post CCRT LS-SCLC)
- Is There ANY Role for TRT in ES-SCLC?
- Where Do ADCs Fit Into the Treatment Landscape for SCLC? Should we add DUAL payloads?
- What is the Role for Neuroendocrine Subtyping & Biomarkers in SCLC?
- With This Plethora of Active Treatments for SCLC – How Do We Sequence Therapies?

Shields Lab

Small Cell SMASHERS

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