Small Cell Lung Cancer

Triparna Sen, PhD

Associate Professor,
Director, Lung Cancer PDX Program,
Department of Oncological Sciences,
Tisch Cancer Institute,
Icahn School of Medicine at Mount Sinai.

Updates in Cancer Therapies,
December 6 and 7, 2024, Miami, USA.

Icahn School of Medicine at Mount Sinai

SCLC- Leading causes of US cancer mortality

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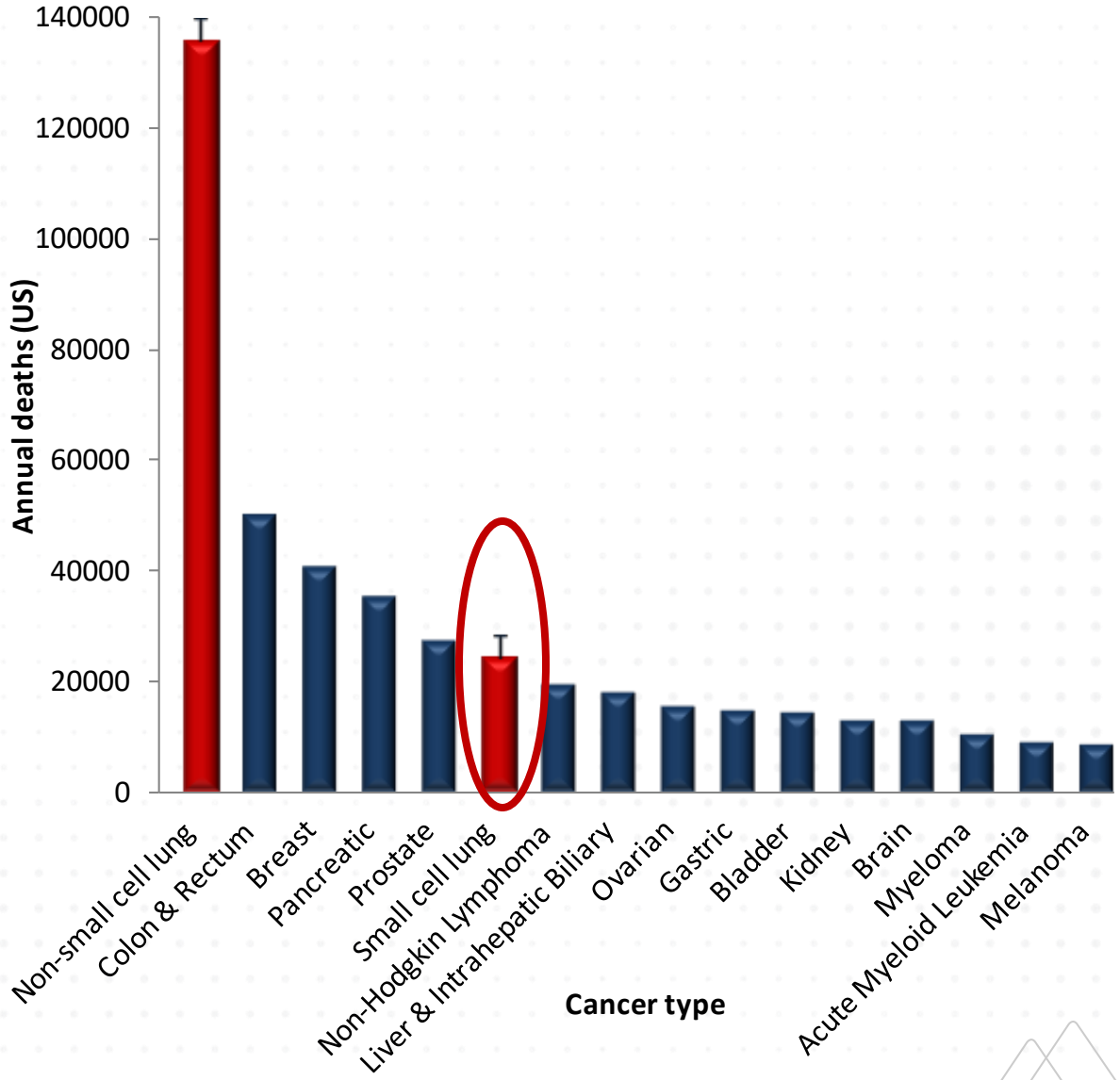
- SCLC accounts for approximately 15% of all lung cancer diagnoses worldwide
- High-grade neuroendocrine tumor
- Majority of patients metastatic at diagnosis

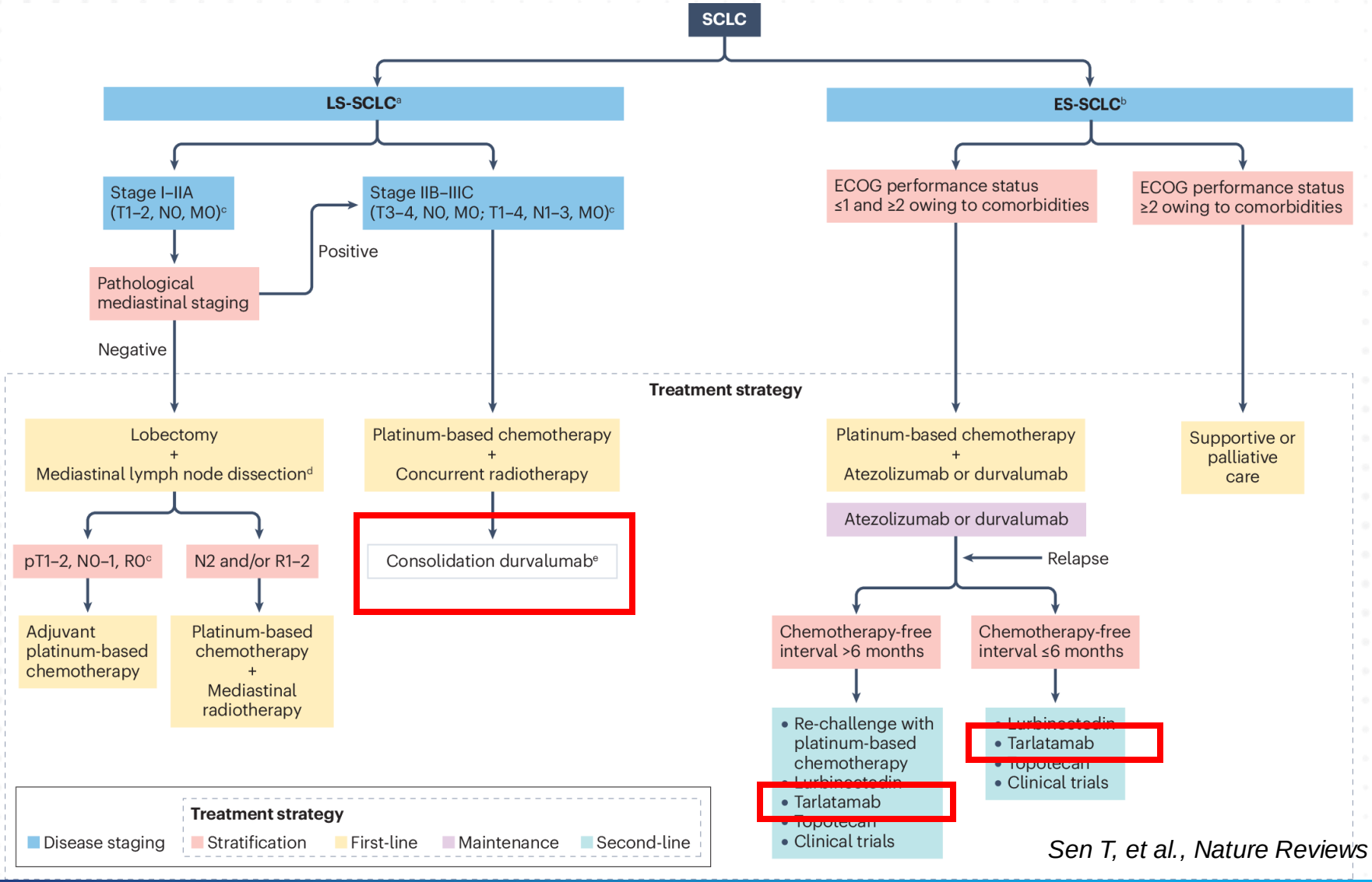
Far too many patients succumb to SCLC



Sen T, et al., Nature Reviews Clinical Oncology, 2024

Management of patients with small-cell lung cancer (SCLC) as of 2024

Promising changes but still limited progress



Sen T, et al., Nature Reviews Clinical Oncology, 2024

OVERVIEW

Small Cell Lung Cancer

- Recent Advancements in Treatment
    - Limited-Stage
    - Extensive-Stage
- Emerging Trials & Novel Targets
- Biology & Biomarkers in SCLC

Consolidation Durvalumab after Concurrent ChemoXRT

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

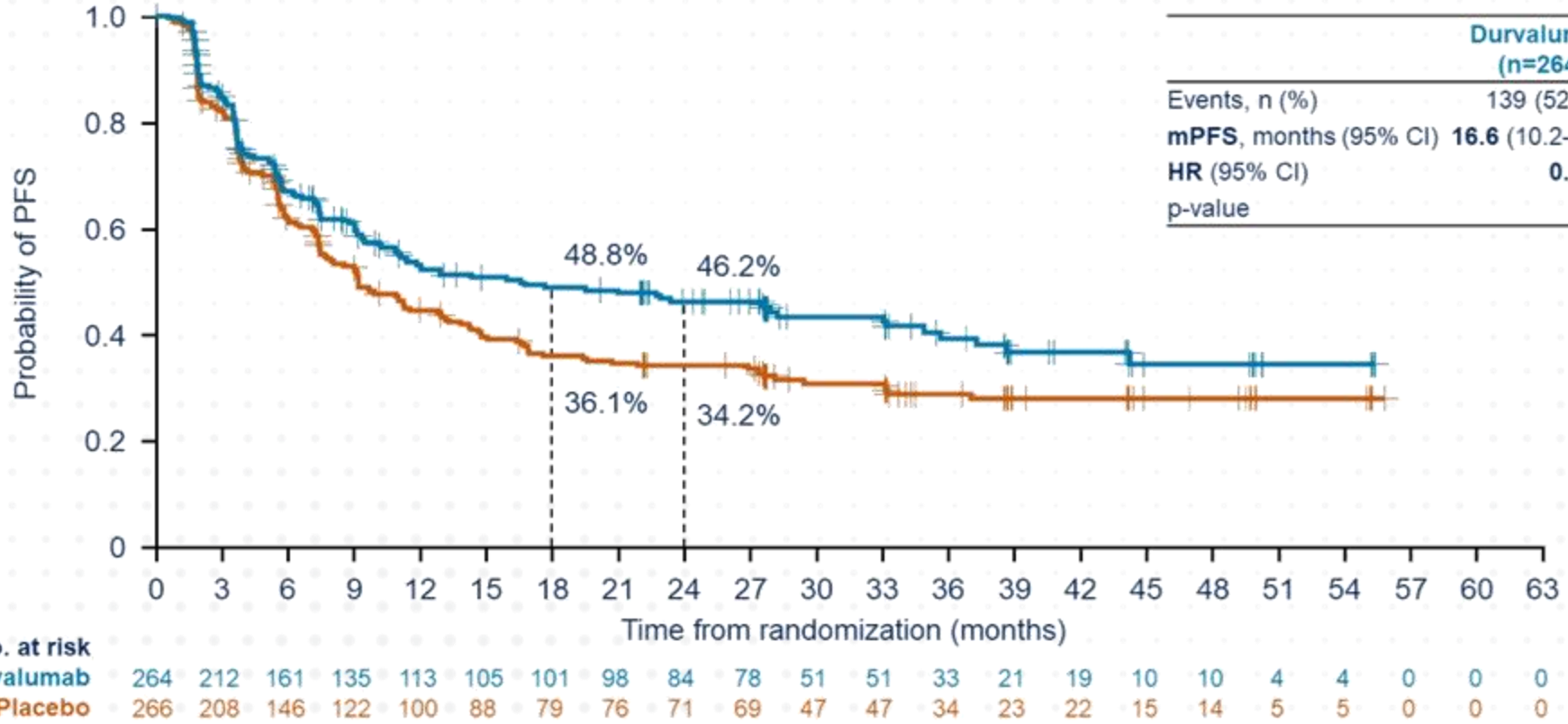
*cCRT and PCI treatment, if received per local standard of care, must have been completed within 1–42 days prior to randomization.
†If disease control was achieved and no additional benefit was expected with an additional cycle of chemotherapy, in the opinion of the investigator.
‡The first 600 patients 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.

Consolidation Durvalumab Post-CCRT Improves PFS

Progression-free survival* (dual primary endpoint)

- Median duration of follow up in censored patients: 27.6 months (range 0.0–55.8)



	Durvalumab (n=264)	Placebo (n=266)
Events, n (%)	139 (52.7)	169 (63.5)
mPFS, months (95% CI)	**16.6** (10.2–28.2)	**9.2** (7.4–12.9)
HR (95% CI)	**0.76** (0.61–0.95)	
p-value	0.0161	

No. at risk																						
Durvalumab	264	212	161	135	113	105	101	98	84	78	51	51	33	21	19	10	10	4	4	0	0	0
Placebo	266	208	146	122	100	88	79	76	71	69	47	47	34	23	22	15	14	5	5	0	0	0

*By BICR per RECIST v1.1.

PFS was analyzed using a stratified log-rank test adjusted for disease stage (I/II vs III) and receipt of PCI (yes vs no). The significance level for testing PFS at this interim analysis was 0.00184 (2-sided) at the 0.5% level, and 0.02805 (2-sided) at the overall 5% level. Statistical significance for PFS was achieved through the recycling multiple testing procedure framework and testing at the 5% (2-sided) alpha level (adjusted for an interim and final analysis).

2024 ASCO ANNUAL MEETING #ASCO24

PRESENTED BY: Dr David R. Spigel

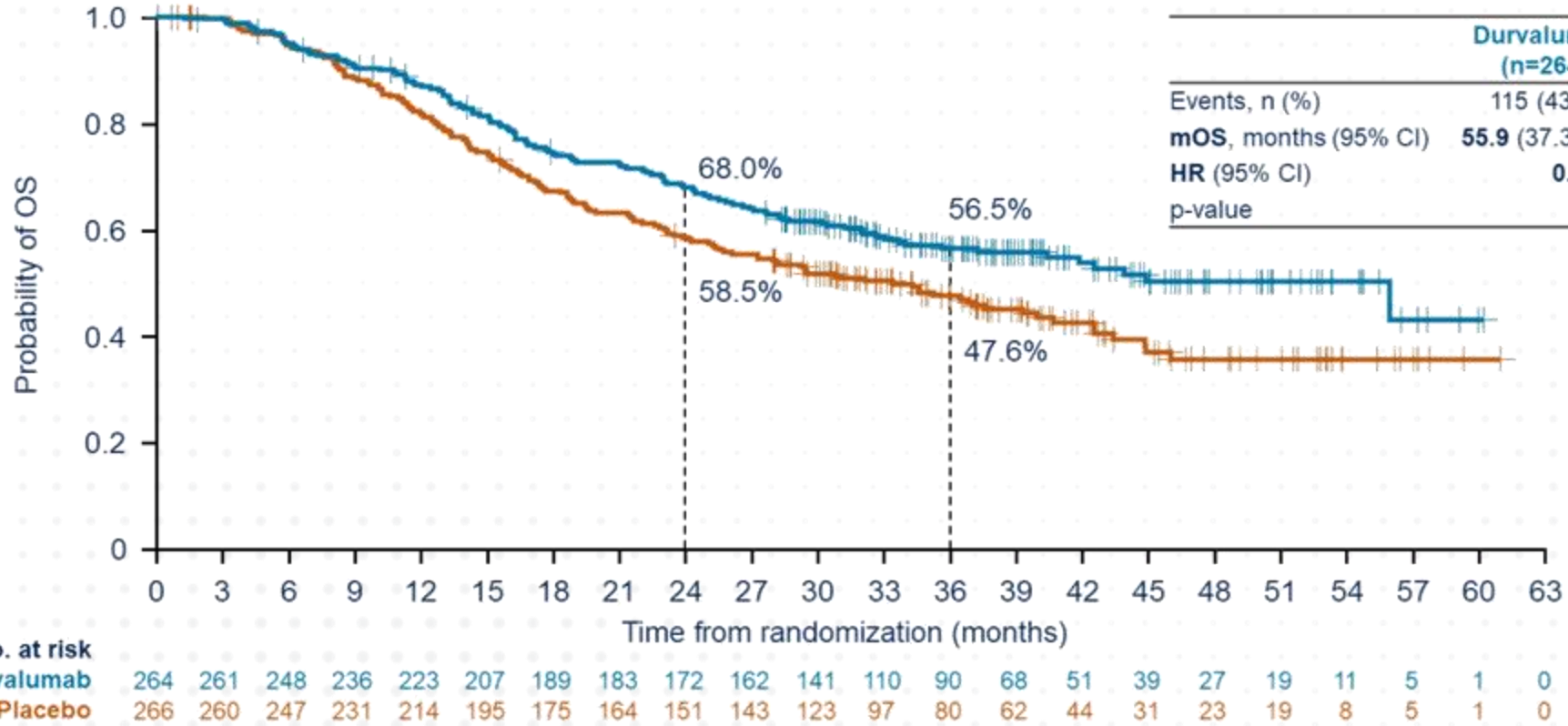
mPFS, median PFS.

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

Consolidation Durvalumab Post-CCRT Improves OS

Overall survival (dual primary endpoint)

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



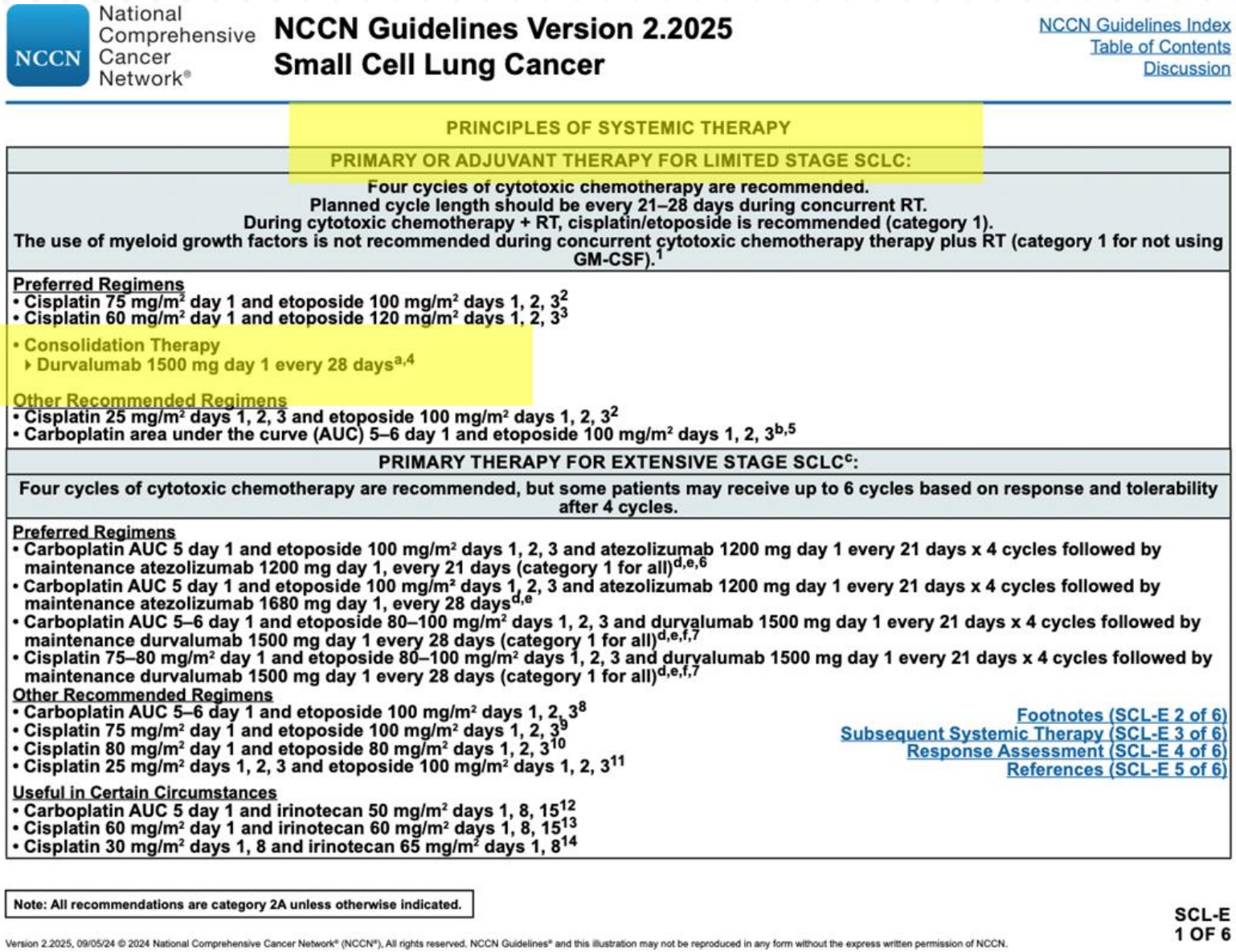
	Durvalumab (n=264)	Placebo (n=266)
Events, n (%)	115 (43.6)	146 (54.9)
mOS, months (95% CI)	**55.9** (37.3–NE)	**33.4** (25.5–39.9)
HR (95% CI)	**0.73** (0.57–0.93)	
p-value	0.0104	

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.

A New Standard of Care for Limited-Stage SCLC



National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2025
Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY

PRIMARY OR ADJUVANT THERAPY FOR LIMITED STAGE SCLC:

Four cycles of cytotoxic chemotherapy are recommended.
Planned cycle length should be every 21–28 days during concurrent RT.
During cytotoxic chemotherapy + RT, cisplatin/etoposide is recommended (category 1).
The use of myeloid growth factors is not recommended during concurrent cytotoxic chemotherapy therapy plus RT (category 1 for not using GM-CSF).[1]

Preferred Regimens
- Cisplatin 75 mg/m² day 1 and etoposide 100 mg/m² days 1, 2, 3[2]
- Cisplatin 60 mg/m² day 1 and etoposide 120 mg/m² days 1, 2, 3[3]
- Consolidation Therapy
  - Durvalumab 1500 mg day 1 every 28 days[a,4]

Other Recommended Regimens
- Cisplatin 25 mg/m² days 1, 2, 3 and etoposide 100 mg/m² days 1, 2, 3[2]
- Carboplatin area under the curve (AUC) 5–6 day 1 and etoposide 100 mg/m² days 1, 2, 3[b,5]

PRIMARY THERAPY FOR EXTENSIVE STAGE SCLC[c]:

Four cycles of cytotoxic chemotherapy are recommended, but some patients may receive up to 6 cycles based on response and tolerability after 4 cycles.

Preferred Regimens
- Carboplatin AUC 5 day 1 and etoposide 100 mg/m² days 1, 2, 3 and atezolizumab 1200 mg day 1 every 21 days x 4 cycles followed by maintenance atezolizumab 1200 mg day 1, every 21 days (category 1 for all)[d,e,6]
- Carboplatin AUC 5 day 1 and etoposide 100 mg/m² days 1, 2, 3 and atezolizumab 1200 mg day 1 every 21 days x 4 cycles followed by maintenance atezolizumab 1680 mg day 1, every 28 days[d,e]
- Carboplatin AUC 5–6 day 1 and etoposide 80–100 mg/m² days 1, 2, 3 and durvalumab 1500 mg day 1 every 21 days x 4 cycles followed by maintenance durvalumab 1500 mg day 1 every 28 days (category 1 for all)[d,e,f,7]
- Cisplatin 75–80 mg/m² day 1 and etoposide 80–100 mg/m² days 1, 2, 3 and durvalumab 1500 mg day 1 every 21 days x 4 cycles followed by maintenance durvalumab 1500 mg day 1 every 28 days (category 1 for all)[d,e,f,7]

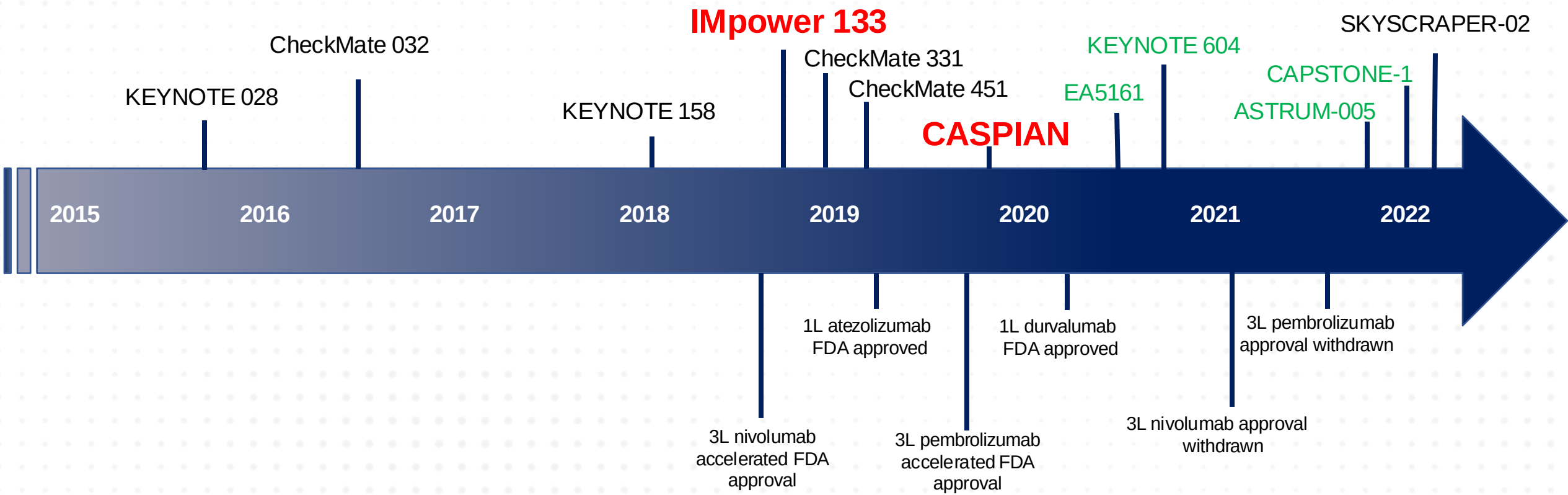
Other Recommended Regimens
- Carboplatin AUC 5–6 day 1 and etoposide 100 mg/m² days 1, 2, 3[8]
- Cisplatin 75 mg/m² day 1 and etoposide 100 mg/m² days 1, 2, 3[9]
- Cisplatin 80 mg/m² day 1 and etoposide 80 mg/m² days 1, 2, 3[10]
- Cisplatin 25 mg/m² days 1, 2, 3 and etoposide 100 mg/m² days 1, 2, 3[11]

Useful in Certain Circumstances
- Carboplatin AUC 5 day 1 and irinotecan 50 mg/m² days 1, 8, 15[12]
- Cisplatin 60 mg/m² day 1 and irinotecan 60 mg/m² days 1, 8, 15[13]
- Cisplatin 30 mg/m² days 1, 8 and irinotecan 65 mg/m² days 1, 8[14]

Footnotes (SCL-E 2 of 6)
Subsequent Systemic Therapy (SCL-E 3 of 6)
Response Assessment (SCL-E 4 of 6)
References (SCL-E 5 of 6)

Note: All recommendations are category 2A unless otherwise indicated.

Checkpoint Inhibitors and SCLC



Adapted from Sen T, et al., Nature Reviews Clinical Oncology, 2024

How are we doing with extensive-stage SCLC

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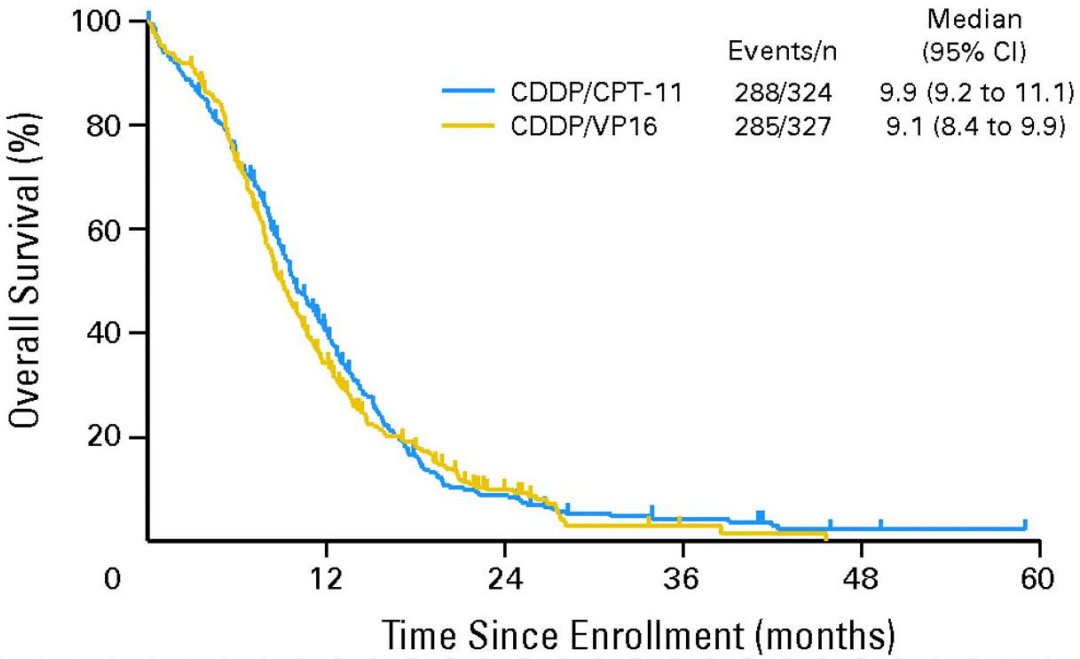
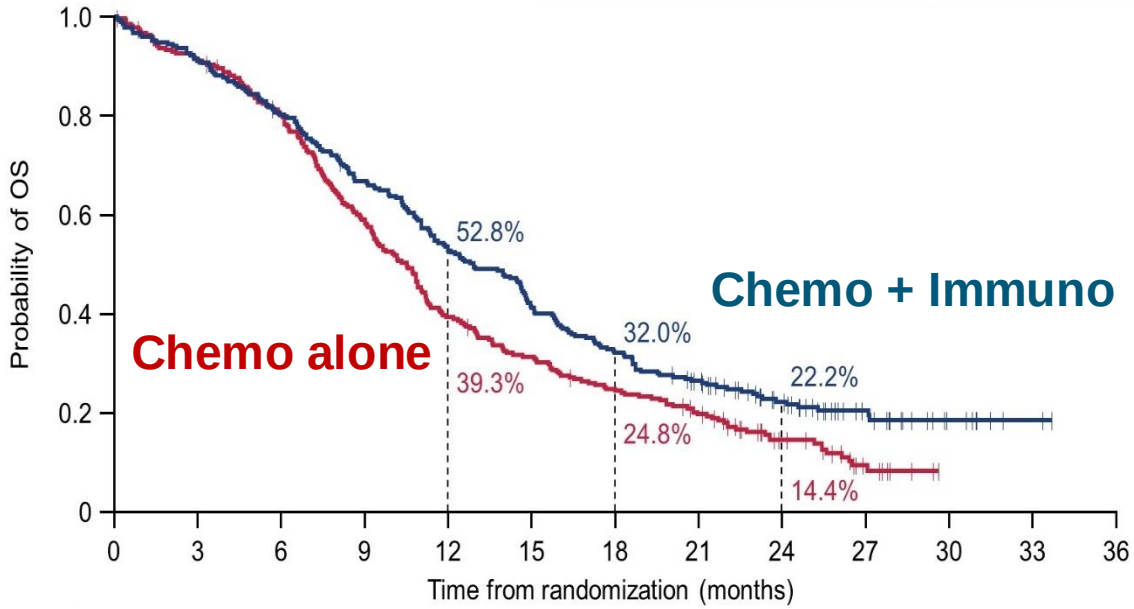
Where we were….



Where we are….



2009

Comparison of two platinum doublet regimens

- Three-year survival <5%
- Essentially no long-term survivors

Lara et al., *JCO, 2009*

2022

Comparison of platinum doublet with or without IO

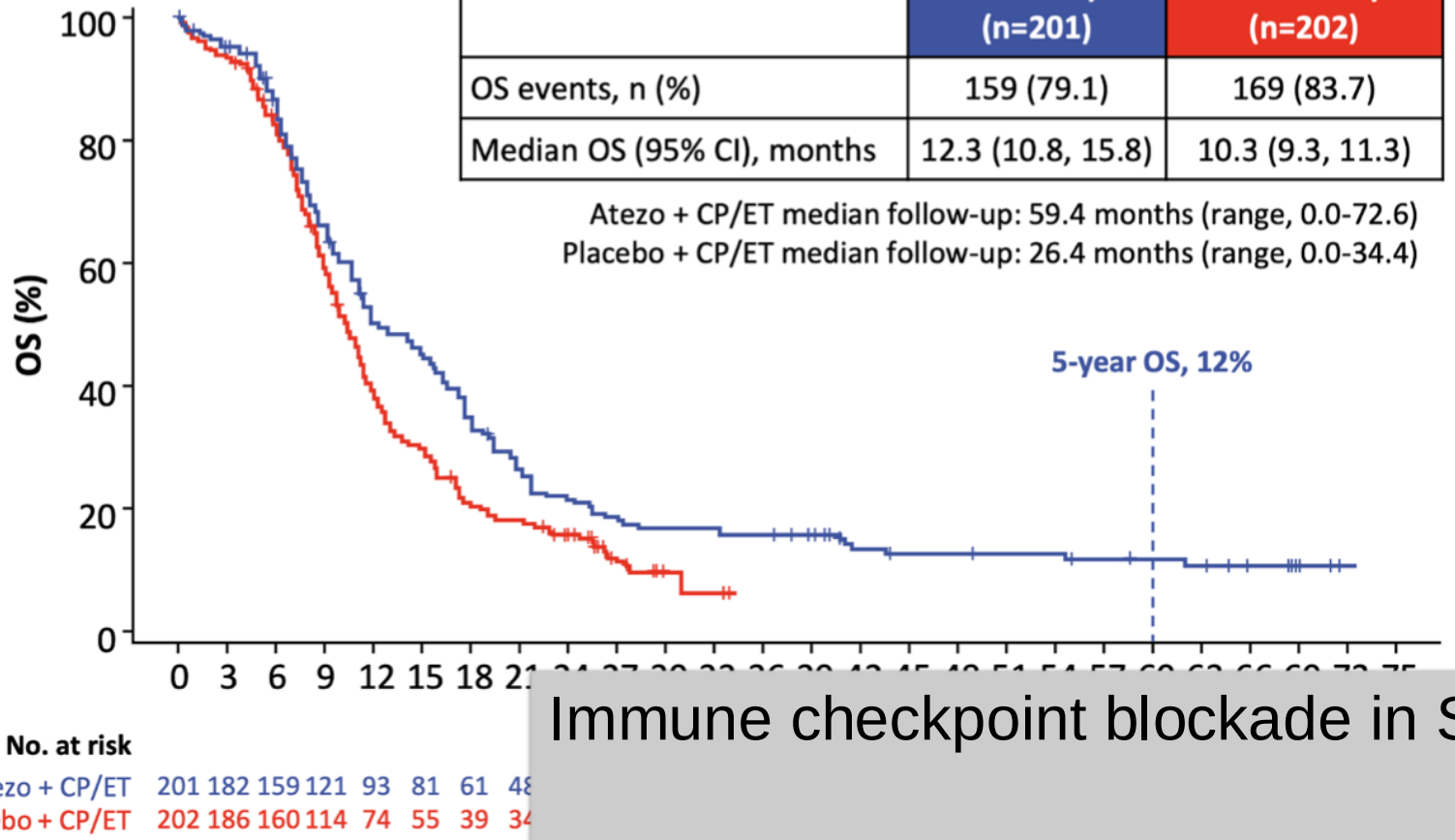
- Three-year survival 17.6 vs 5.8%
- Curves flatten out

Horn et al., *N Engl J Med* 2018; Paz-Ares et al., *Lancet* 2019

IMbrella A: Extension Study to IMpower133

	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]

5Y OS improved to 12% with tezolizumab in ES-SCLC

Immune checkpoint blockade in SCLC

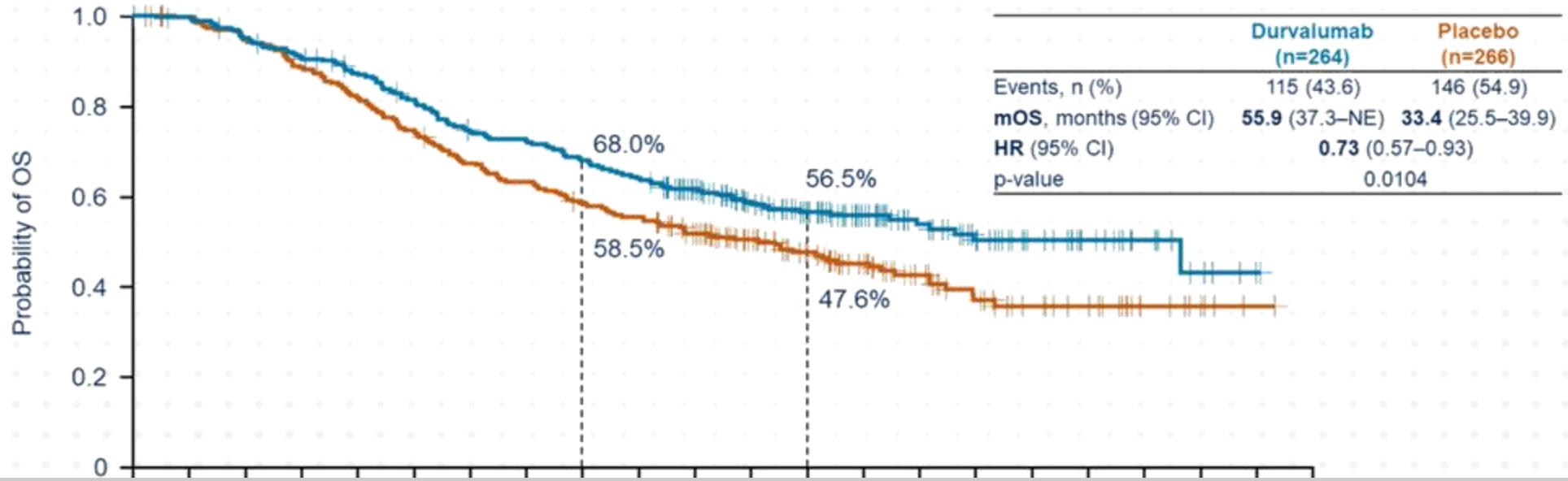
- They work
- They have a role

Liu, et al. *WCLC*. 2023.

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

Overall survival (dual primary endpoint)

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



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HR (95% CI)	**0.73** (0.57–0.93)	
p-value	0.0104	

Abscopal effect?
Upregulation of MHC Class I?
Enrichment for a particular NE subtype?
Tumor-immune co-evolution…

Cheng et al., NEJM, 2024

Lurbinectedin as a second line therapy for SCLC

- 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)
- **Accelerated FDA approval (June 2020)**

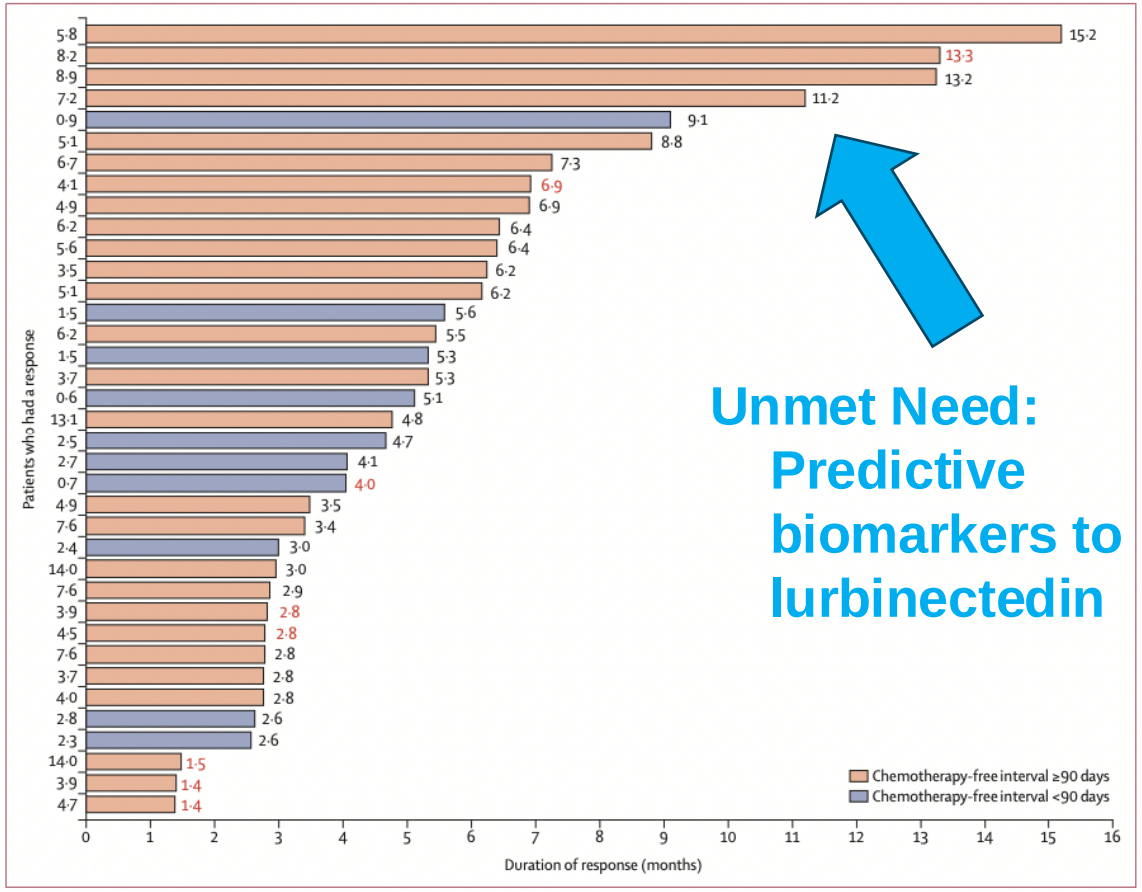

Figure 1: **Duration of response by investigator assessment**
Each bar represents a patient with SCLC who responded to treatment (n=37). Data shown on the left of each bar are the chemotherapy-free interval (months); data shown on the right of each bar are the duration of response (0 is the time of starting 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.

Lurbinectedin augments the anti-tumor effect of osimertinib in transformed SCLC

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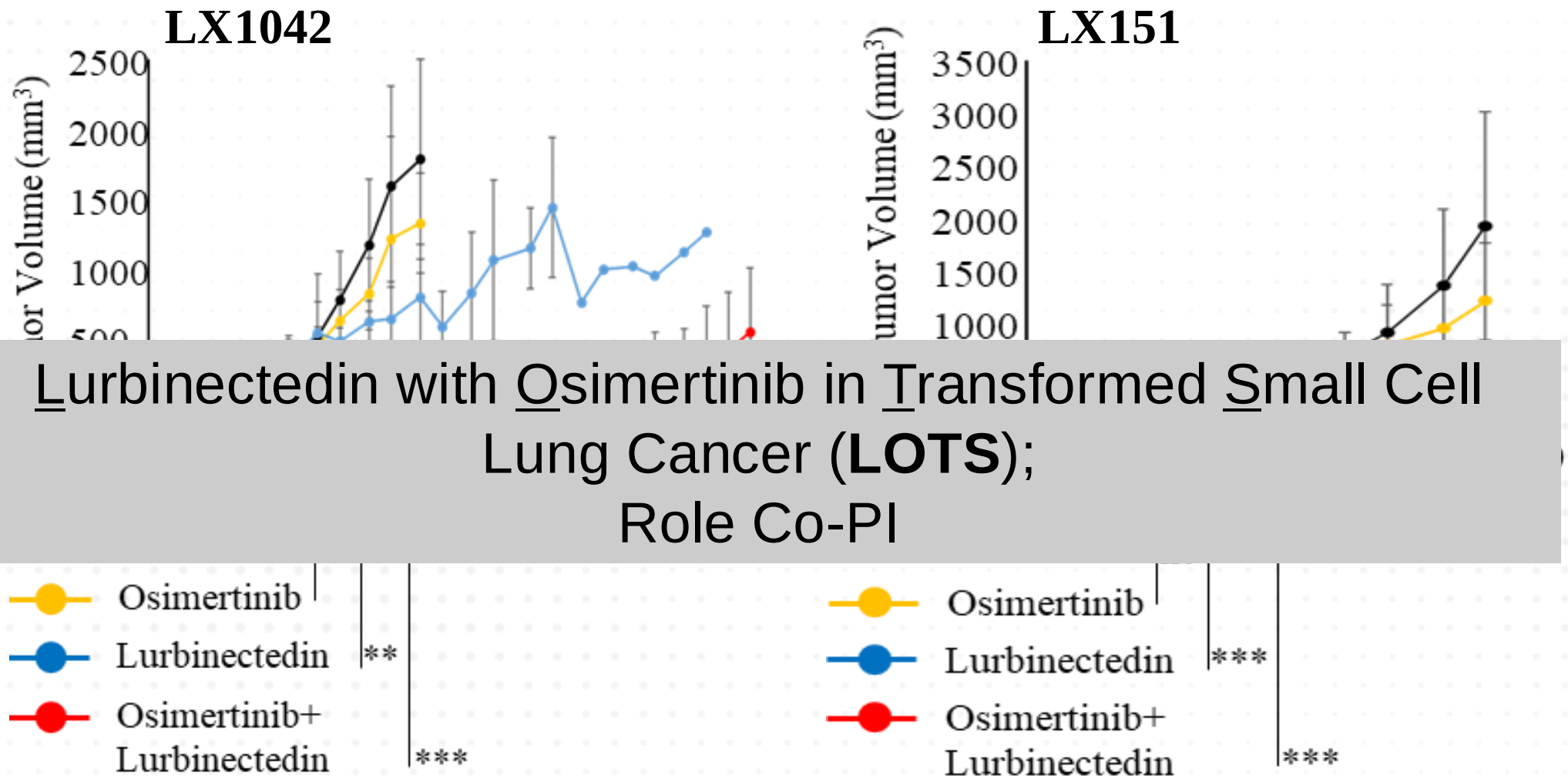

Lurbinectedin with Osimertinib in Transformed Small Cell Lung Cancer (**LOTS**);
Role Co-PI

Chakraborty et al., Clinical Cancer Research, 2023

IMforte: Addition of Lurbinectedin to Atezolizumab Maintenance

Jazz Pharmaceuticals Announces Statistically Significant Overall Survival and Progression-Free Survival Results for Zepzelca® (lurbinectedin) and Atezolizumab Combination in First-Line Maintenance Therapy for Extensive-Stage Small Cell Lung Cancer

October 15, 2024

Download PDF

Jazz plans to submit supplemental New Drug Application in first half of 2025 for this combination therapy as a first-line maintenance treatment for ES-SCLC

Lurbinectedin and PD-L1 causes significant tumor regression in the maintenance setting

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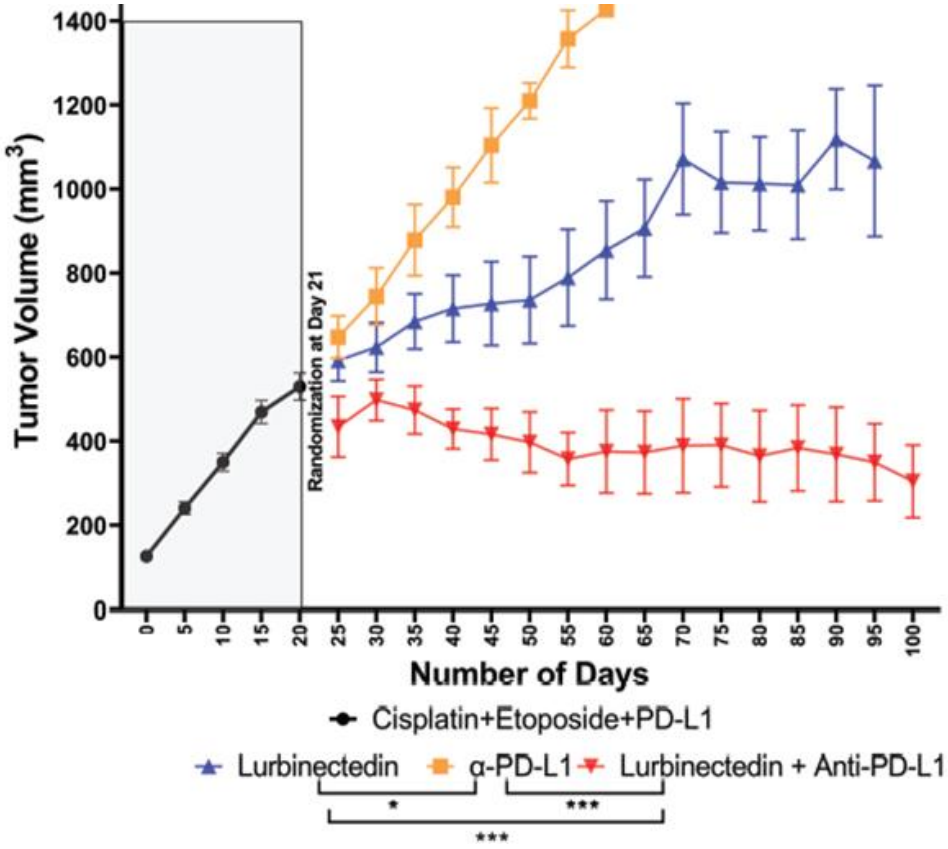
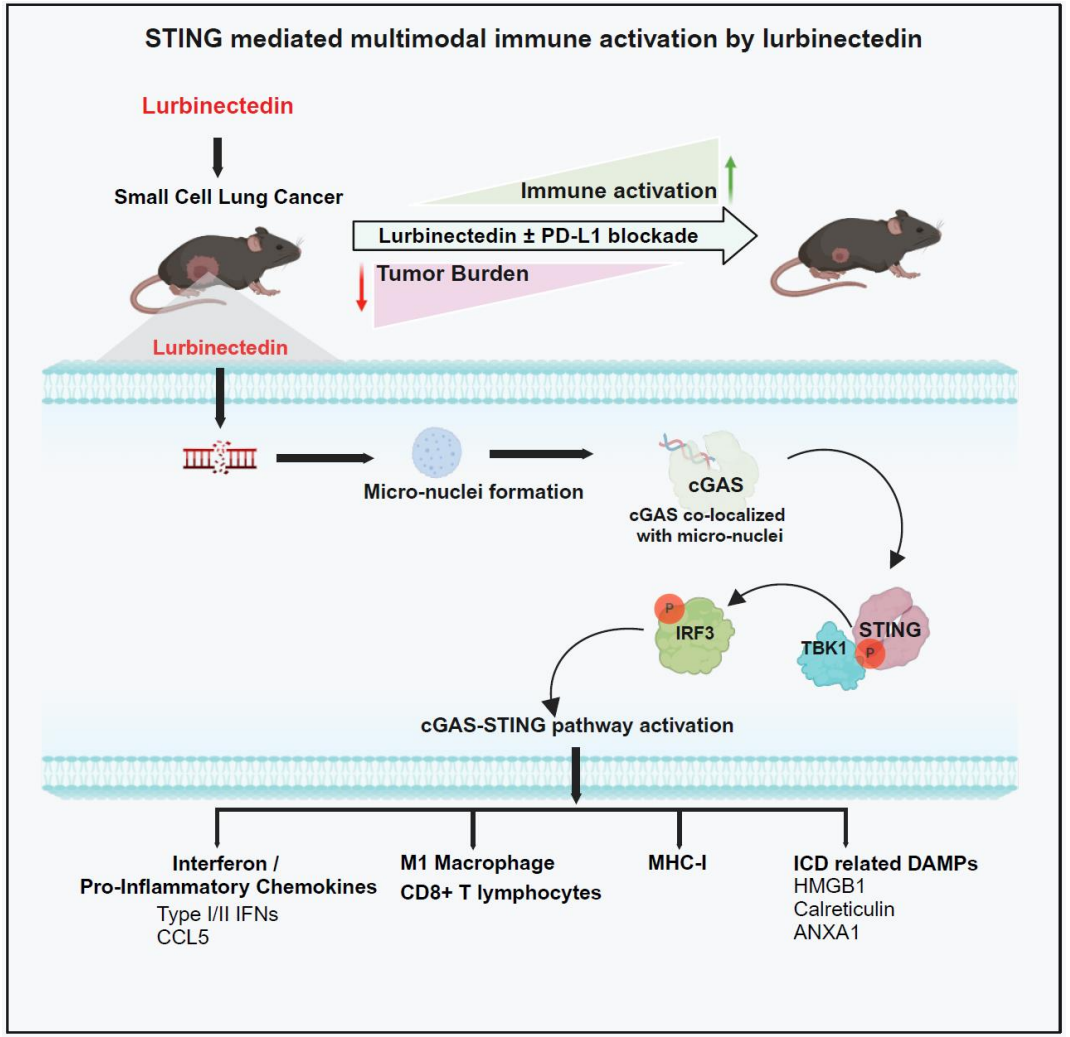




Subhamoy Chakraborty

Chakraborty et al., Cell Reports Medicine, 2024

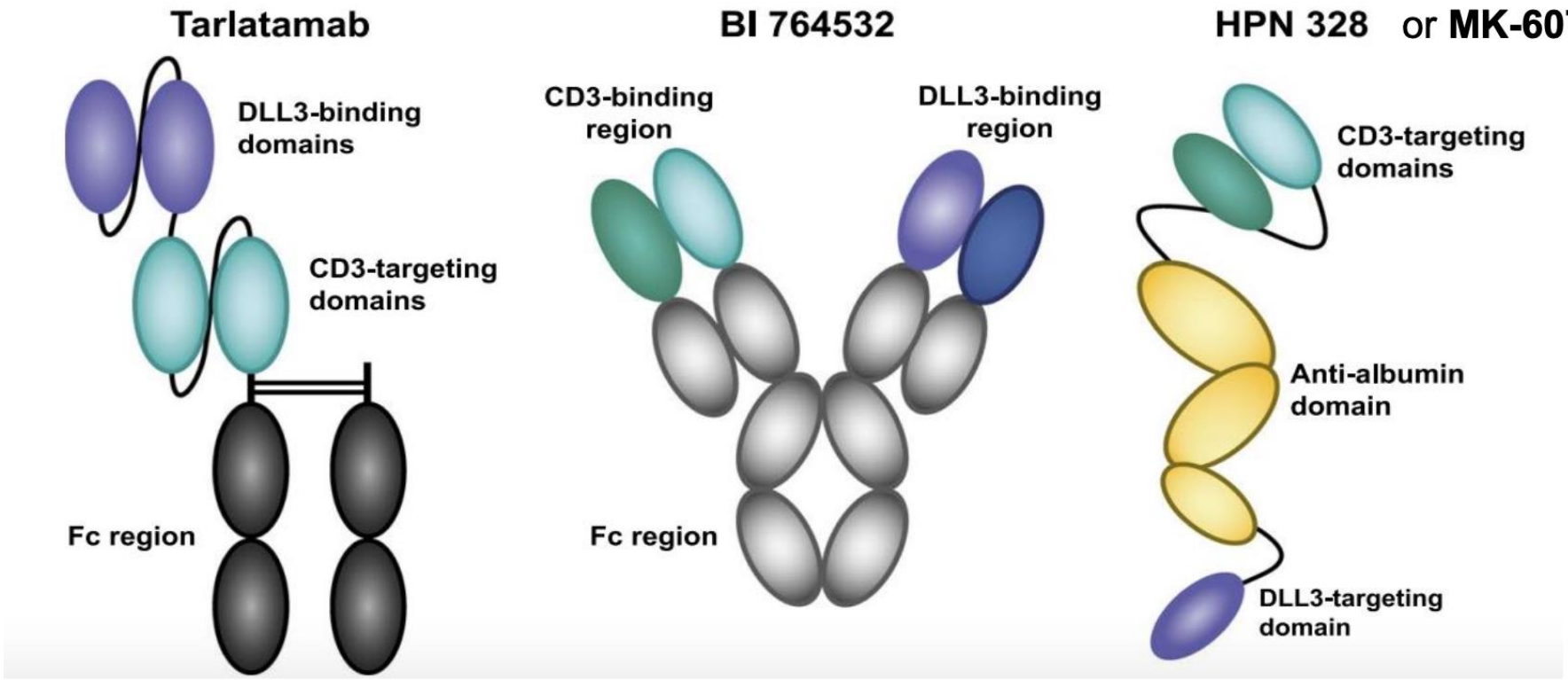
OVERVIEW

Small Cell Lung Cancer

- Recent Advancements in Treatment
    - Limited-Stage
    - Extensive-Stage
- Emerging Trials & Novel Targets
- Biology & Biomarkers in SCLC

DLL3 BiTE/TriTEs in ES-SCLC

Structure of DLL3-targeting TCEs in development



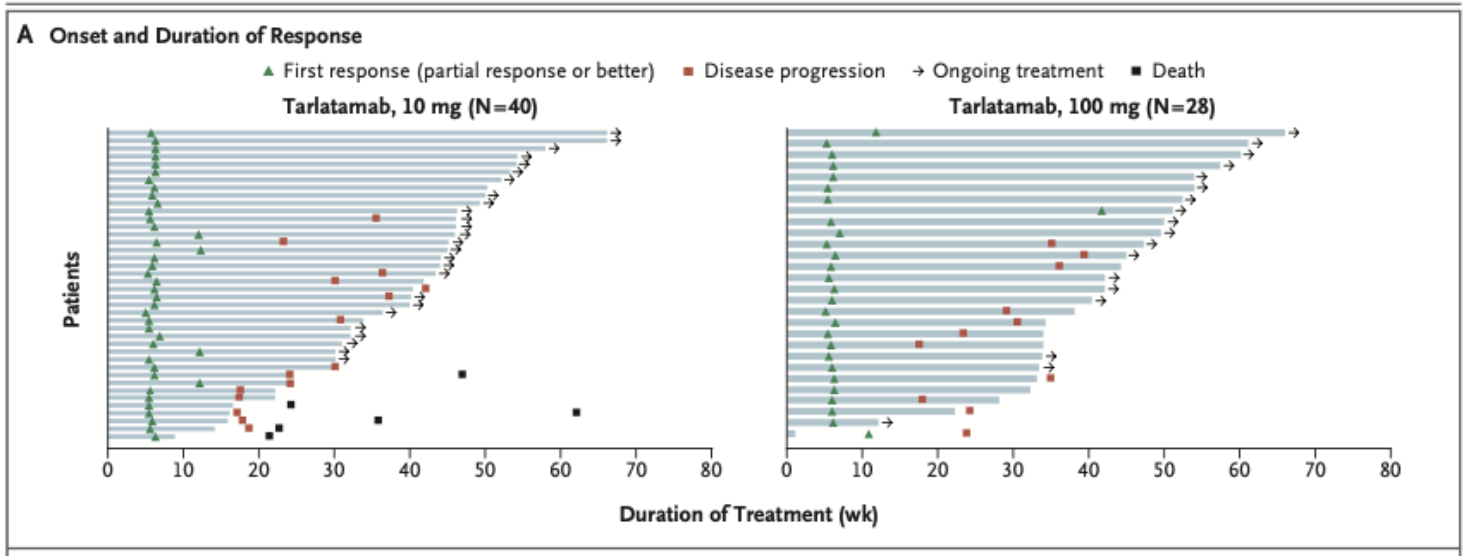
Rudin et al. Journal of Hematology & Oncology (2023) 16:66

Tarlatamab as a second line therapy for SCLC

- 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

- **Accelerated FDA approval (May 2024)**



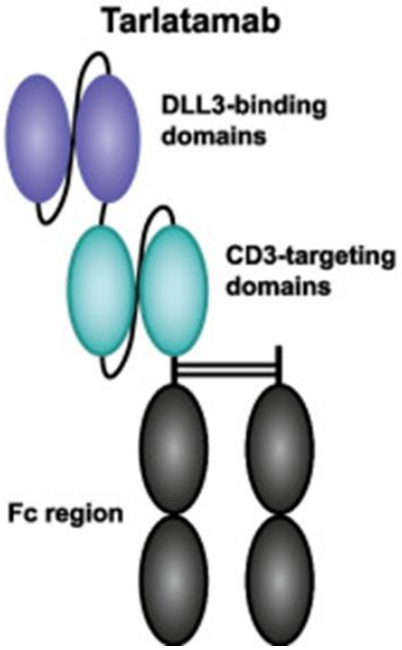
Responses to tarlatamab are durable

Ahn, et al. *NEJM*. 2023.

Tarlatamab Addition to 1L ChemoIO Maintenance

DeLLphi-303: Tarlatamab with PD-L1 Inhibitor as 1LM

DeLLphi 303



- Phase 1b, multicenter, open-label study (NCT05361395)

1L Chemo-IO

Platinum-etoposide + PD-L1 inhibitor

(4-6 cycles)

Enrollment

Key Inclusion Criteria

- No disease progression following 4-6 cycles of platinum-etoposide + PD-L1 inhibitor
- Eligible if no access to 1L PD-L1 inhibitor
- Prior treatment for LS-SCLC permitted
- ECOG PS 0-1
- Treated and asymptomatic brain metastases allowed
- DLL3 positivity not required

1L Maintenance

Non-randomized

Switching to different PD-L1 inhibitor permitted

- **Tarlatamab (10 mg IV Q2W)* + Atezolizumab (1680 mg IV Q4W)**
- **Tarlatamab (10 mg IV Q2W)* + Durvalumab (1500 mg IV Q4W)**

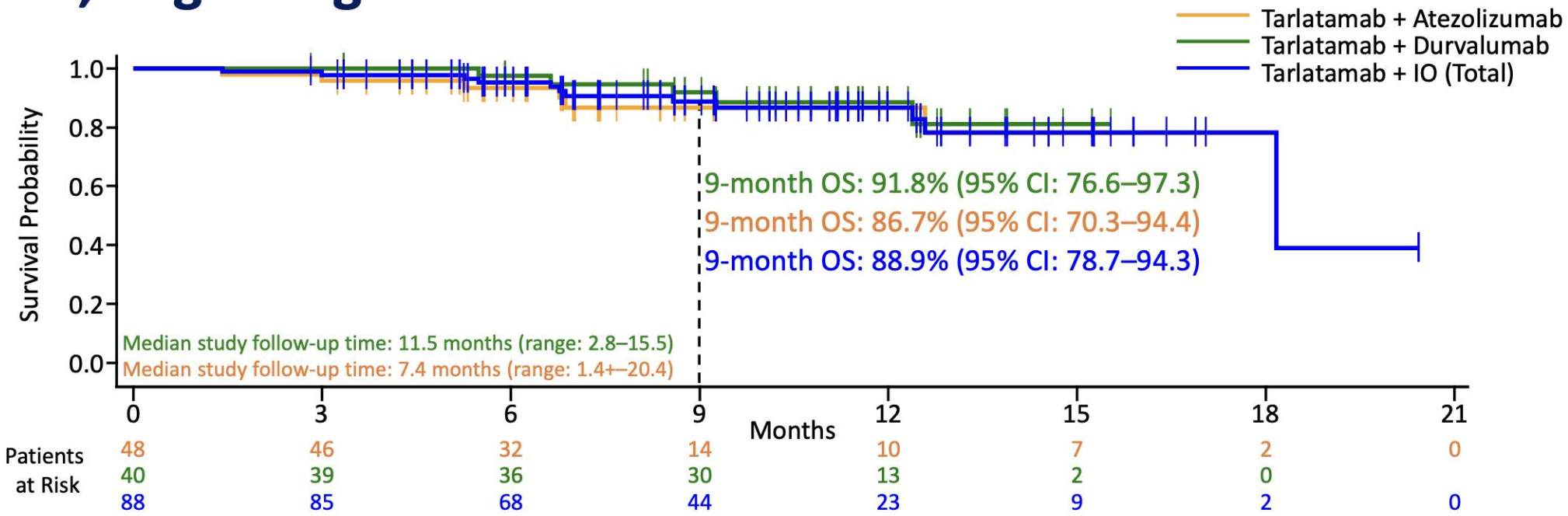
- Must initiate C1D1 of maintenance phase within 8 weeks of the start of the last cycle of 1L chemo-immunotherapy
- Median follow-up time (N = 88): 10.0 months (range: 1.4+–20.4)

Primary Endpoints†: Dose-limiting toxicities, treatment-emergent / treatment-related adverse events (TEAEs, TRAEs)
Secondary Endpoints‡: Disease control and PFS per local RECIST 1.1 assessment, OS

Data cutoff was May 31, 2024. *Tarlatamab was initiated with step dosing: 1 mg on Day 1, followed by 10 mg on Days 8, 15, and Q2W thereafter. †Also includes vital signs, electrocardiograms, and clinical laboratory tests. ‡Also includes objective response, duration of response, and serum concentrations of tarlatamab. **+,** censored; **1L,** first-line; **1LM,** first-line maintenance; **C1D1,** cycle 1 day 1; **chemo,** chemotherapy; **DLL3,** delta-like ligand 3; **ECOG PS,** Eastern Cooperative Oncology Group performance status; **IO,** immuno-oncology agent; **IV**, intravenous; **LS**, limited-stage; **OS,** overall survival; **PD-L1**, programmed death-ligand 1; **Q2W**, once every two weeks; **Q4W**, once every four weeks; **RECIST,** response evaluation criteria in solid tumors; **SCLC**, small cell lung cancer.

Tarlatamab Addition to 1L ChemoIO Maintenance

OS, beginning from 1L maintenance



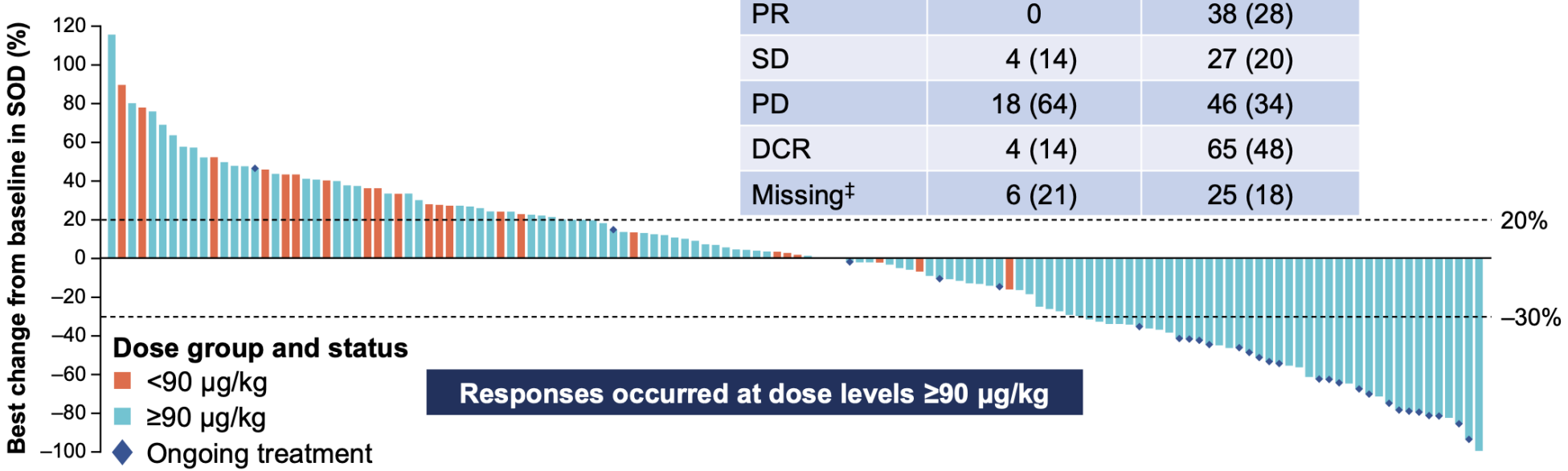
After a median time from 1L chemoimmunotherapy to 1LM of 3.6 months, tarlatamab with a PD-L1 inhibitor as 1LM showed a 9-month OS of 89%.

+, 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

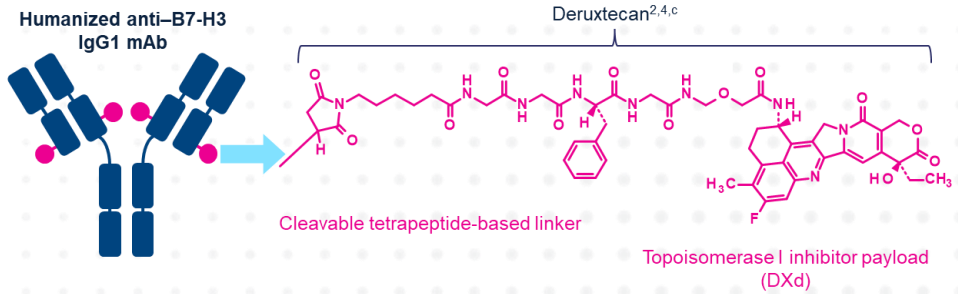
Data cut-off: Feb 21, 2024
DCR, disease control rate; PD, progressive disease; PR, partial response; RECIST v.1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease; SOD, sum of diameters

Antibody Drug Conjugates in ES-SCLC

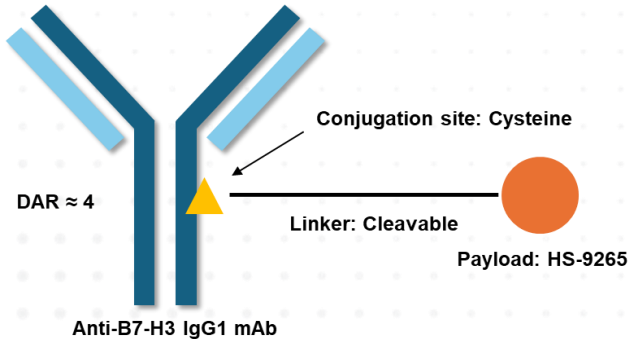
Target	Drug	Phase	NCT number
B7-H3	Ifinatamab deruxtecan	III	NCT06203210
		I/II	NCT04145622
	MGC018	II	NCT06227546
	HS-20093	I	NCT05276609
B7-H3	Mirzotamab clezutoclax plus paclitaxel or docetaxel	I	NCT03595059
TROP2, ATR	Sacituzumab govitecan plus berzosertib	I/II	NCT04826341
TROP2	SKB264	I/II	NCT04152499
	Dapotomab deruxtecan	I	NCT03401385
SEZ6	ABBV-706, cisplatin, carboplatin and budigalimab	I	NCT05599984
	ABBV-011 ± budigalimab	I	NCT03639194

Sen T, et al., Nature Reviews Clinical Oncology, 2024

Ifinatamab deruxtecan (I-DXd)



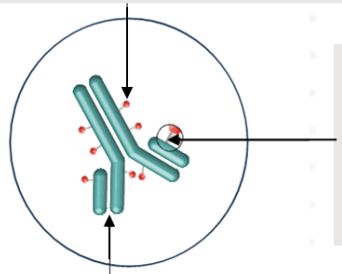
Sacituzumab govitecan



- High permeability
- High potency of tumor cell killing
- High clearance in vivo
- Good bystander effect

HS-20093 (B7-H3-directed ADC)

SN-38 payload
- SN-38 is more potent than the parent compound, irinotecan (Topo-1 inhibitor)
- SN-38 is rapidly internalized and efficiently released to the tumor with minimized effect on healthy tissues



Linker for SN-38
- pH-sensitive, hydrolyzable linker for SN-38 release in targeted tumor cells and tumor microenvironment, allowing bystander effect
- High drug-to-antibody ratio (7.6:1)[4]

Humanized anti–Trop-2 antibody
- Binds with high (K_D = 0.3 nM) affinity to Trop-2, an epithelial antigen expressed on many solid tumors[5]

Ifinatamab Deruxtecan (I-DXd) in ES-SCLC

Phase 2 IDeate-Lung01 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) are eligible

R 1:1

Arm 1: I-DXd 8 mg/kg Q3W (n≈40)

Arm 2: I-DXd 12 mg/kg Q3W (n≈40)

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

Stratification:

- 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[c]
- TTR by BICR and inv[c]
- ORR by inv[c]
- Safety
- Pharmacokinetics
- Immmunogenicity

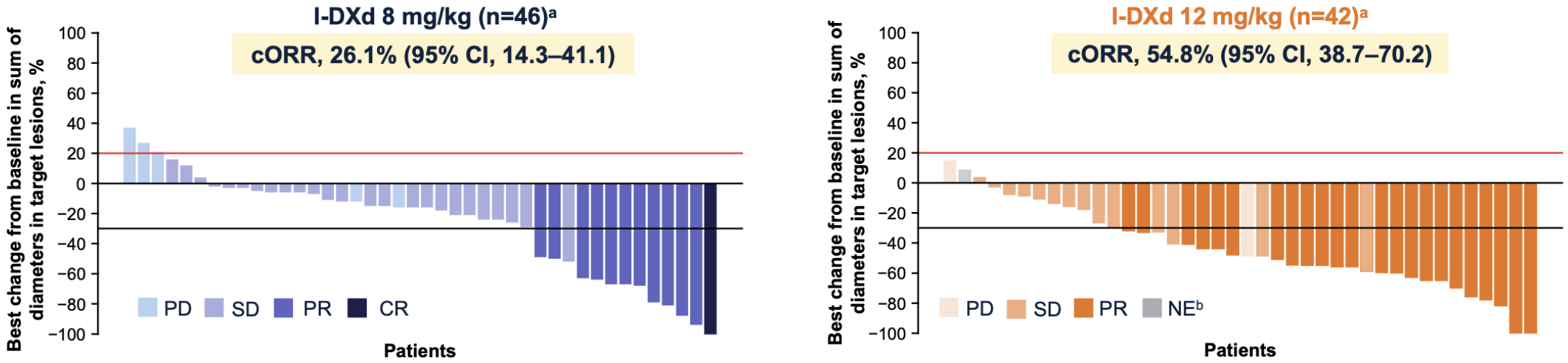
Exploratory analysis:

- Intracranial ORR by BICR[d]

[a]Or local legal age of consent. [b]Patients must also have ≥1 lesion that has not been irradiated and is amenable to biopsy. [c]Per RECIST 1.1. [d]Per CNS RECIST.
2L, second-line; 3L+, third-line and beyond; 4L, fourth-line; BICR, blinded independent central review; CTFI, chemotherapy treatment-free interval; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ES-SCLC, extensive-stage small cell lung cancer; inv, investigator; ORR, objective response rate; OS, overall survival; PBC, platinum-based chemotherapy; PD, progressive disease; PD-(L)1; programmed death (ligand) 1; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; RECIST 1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; RP3D, recommended Phase 3 dose; TTR, time to response.

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)

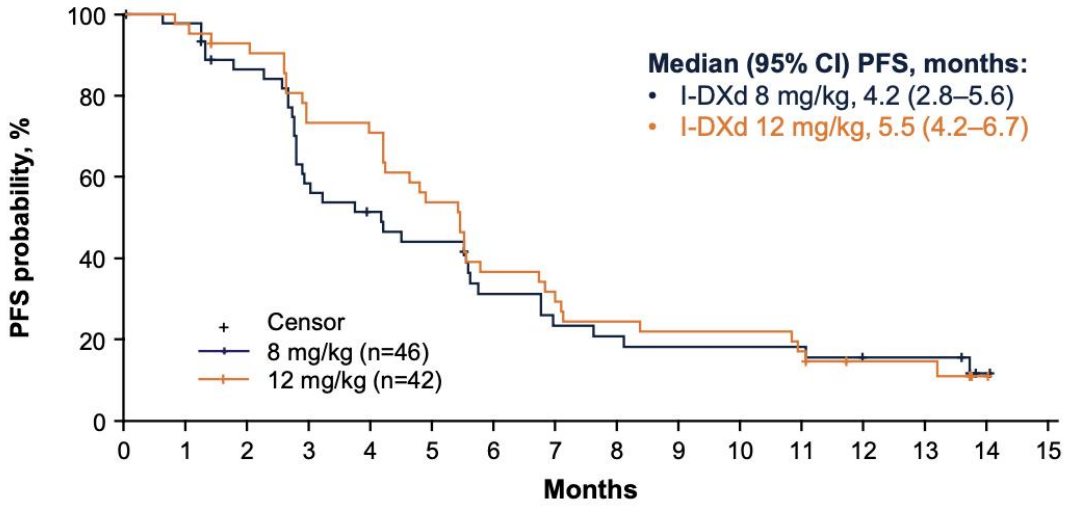
Data cutoff: April 25, 2024. The median follow-up for 8-mg/kg and 12-mg/kg cohorts was 14.6 months (range, 0.6–17.0) and 15.3 months (range, 0.8–20.3) respectively.

[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.

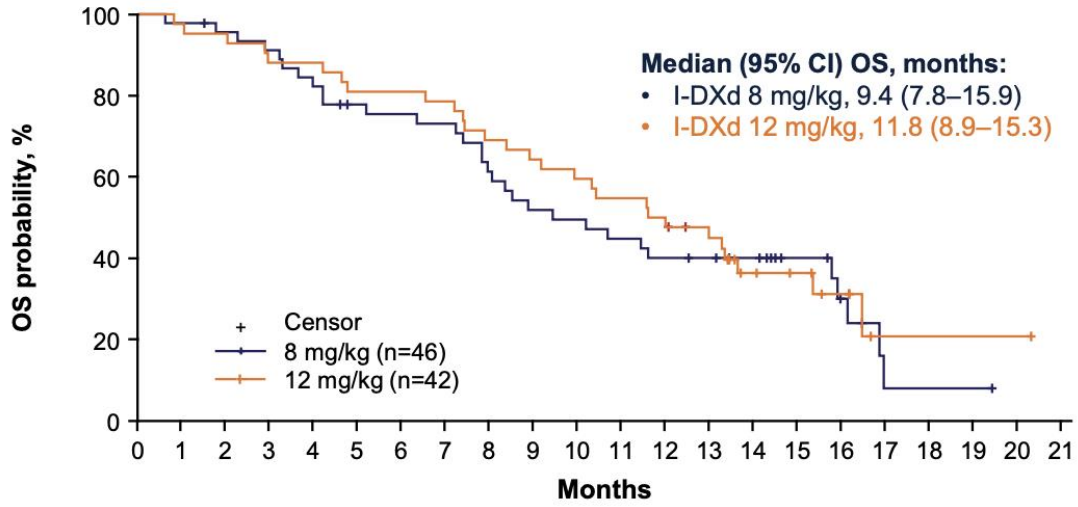
Ifinatamab Deruxtecan (I-DXd) in ES-SCLC

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.

Sacituzumab Govitecan as Second-Line Treatment in Patients With Extensive-Stage Small Cell Lung Cancer

TROPiCS-03 Study Design

- The ongoing, open-label, multicohort, phase 2 TROPiCS-03 study (NCT03964727) is evaluating SG in patients with metastatic or locally advanced solid tumors
  - — A preliminary analysis showed SG has promising antitumor activity and a manageable safety profile in an extensive-stage small cell lung cancer (ES-SCLC) cohort[1]
  - — Here, we report updated results with additional patients and longer follow-up from the ES-SCLC cohort

Key eligibility criteria
- Histologically confirmed ES-SCLC
- Disease progression after no more than 1 prior line of platinum-based chemo and anti–PD-(L)-1 therapy
- Measurable disease per RECIST v1.1
- ECOG PS 0–1
- Stable, treated brain metastases allowed[a]

→ **ES-SCLC cohort** (N = 43) → **SG 10 mg/kg** IV on D1 and D8 21-day cycles (until PD or unacceptable toxicity) → **Survival follow-up**

Primary end points
- ORR (INV[b])

Secondary end points
- DOR, CBR, PFS (INV[b])
- ORR, DOR, CBR, PFS (BICR[b])
- OS
- Safety

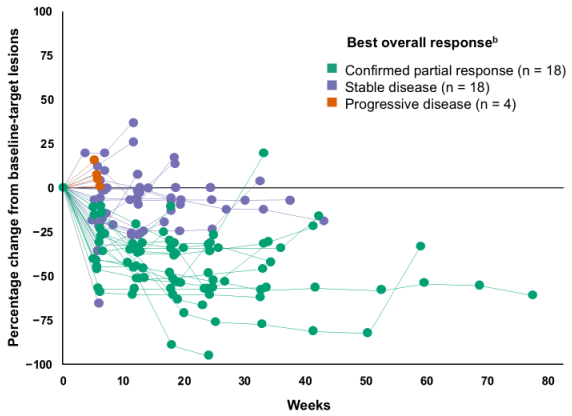
- At data cutoff (8 March 2024), median follow-up was 12.3 (range, 8.1–20.1) months

[a]Patients with stable CNS disease for ≥4 weeks prior to the first study dose and all neurologic symptoms returned to baseline may be included in the study. All patients with carcinomatous meningitis are excluded from the study, regardless of clinical stability. [b]Per RECIST v1.1.
BICR, blinded independent central review; **CBR**, clinical benefit rate; **chemo**, chemotherapy; **CNS**, central nervous system; **D**, day; **DOR**, duration of response; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **ES-SCLC**, extensive-stage small cell lung cancer; **INV**, investigator-assessed; **IV**, intravenous; **ORR**, objective response rate; **OS**, overall survival; **PD**, progressive disease; **PD-(L)1**, programmed death (ligand) 1; **PFS**, progression-free survival; **RECIST v1.1**, Response Evaluation Criteria in Solid Tumors version 1.1; **SG**, sacituzumab govitecan.
1. Dowlati A, et al. Oral presentation ESMO 2023. Abstract #1099MO.

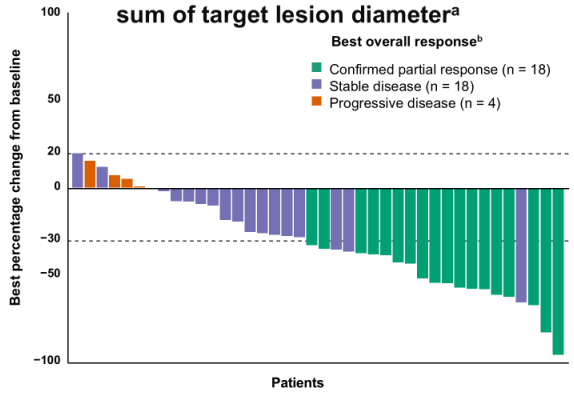
2024 World Conference on Lung Cancer | SEPTEMBER 7-10, 2024 SAN DIEGO, CA USA | #WCLC24 wclc2024.iaslc.org

Efficacy Analyses

Tumor response over time[a]



Best percentage change from baseline in total sum of target lesion diameter[a]



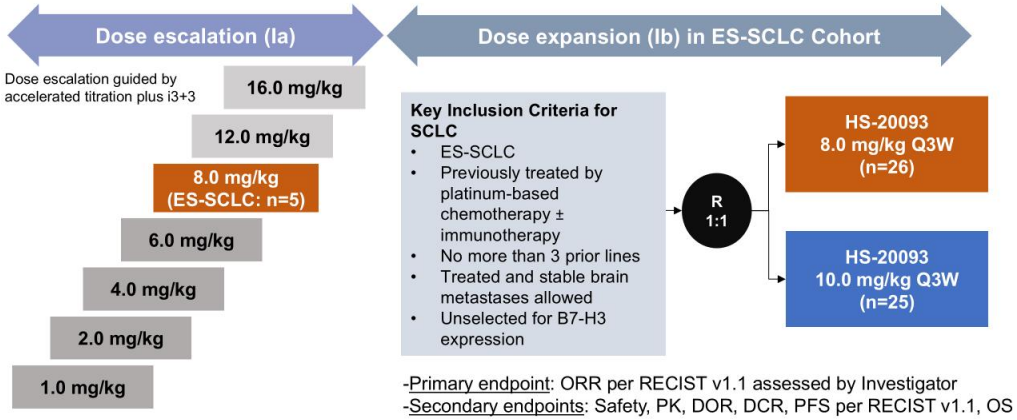
- 76.7% (33/43) of patients had tumor shrinkage
- 48.8% (21/43) of patients had a reduction of >30% in target lesion diameter

[a]By investigator assessment. [b]Three patients without any post-baseline assessments were counted as not assessed for response.

- SG showed promising efficacy as a second-line treatment for patients with ES-SCLC
  - —ORR was 41.9% (95% CI, 27.0–57.9); DOR rate at 6 months was 48.2% (95% CI, 23.9–68.9)
  - —Median PFS was 4.4 months (95% CI, 3.81–6.11) and median OS was 13.6 months (95% CI, 6.57–14.78)
- SG demonstrated antitumor activity in patients with both platinum-resistant (ORR, 35.0%; 95% CI, 15.4–59.2) and platinum-sensitive (ORR, 47.8%; 95% CI, 26.8–69.4) disease

Efficacy and Safety of HS-20093 (B7-H3-directed ADC) in Extensive Stage Small Cell Lung Cancer in A Multicenter, Open-label, Phase 1 Study (ARTEMIS-001)

ARTEMIS-001 STUDY DESIGN



-Primary endpoint: ORR per RECIST v1.1 assessed by Investigator
-Secondary endpoints: Safety, PK, DOR, DCR, PFS per RECIST v1.1, OS

Out of 56 treated pts, 53 pts were evaluable for efficacy (8.0 mg/kg: 31 pts; 10.0 mg/kg: 22 pts), as of 30 June 2024.

Abbreviations: B7-H3, B7 homologous 3; DCR, disease control rate; DoR, duration of response; ES-SCLC, extensive stage small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression free survival; PK pharmacokinetics; Q3W, every 3 weeks.

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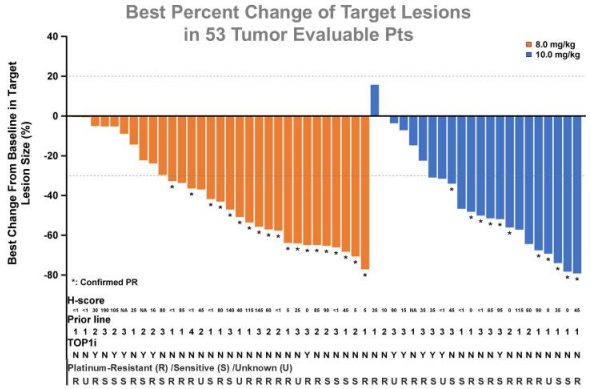
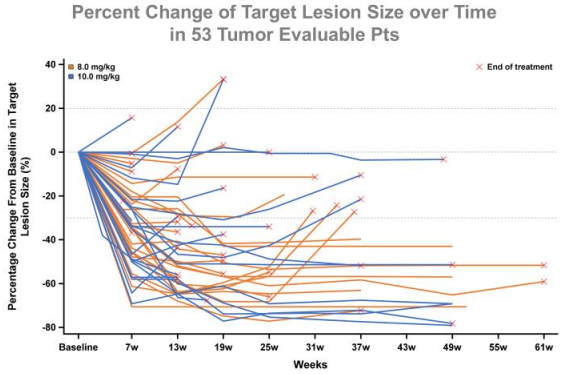
EFFICACY

	8.0 mg/kg (n=31)	10.0 mg/kg (n=22)
ORR, % (95% CI)	61.3 (42.2, 78.2)	50.0 (28.2, 71.8)
DCR, % (95% CI)	80.6 (62.5, 92.5)	95.5 (77.2, 99.9)





Data cut off date: 30 June 2024. Abbreviations: DCR, disease control rate; H-score, histochemistry score of B7-H3 protein. ORR, objective response rate; TOP1i, previously treated by topoisomerase I inhibitor.

- HS-20093 demonstrated encouraging antitumor efficacy in ES-SCLC. The higher overall response rate was observed in 8.0 mg/kg despite more number of pts with brain, liver and bone metastases.

Ongoing Phase 3 SCLC Trials and Global Phase 1 Trial

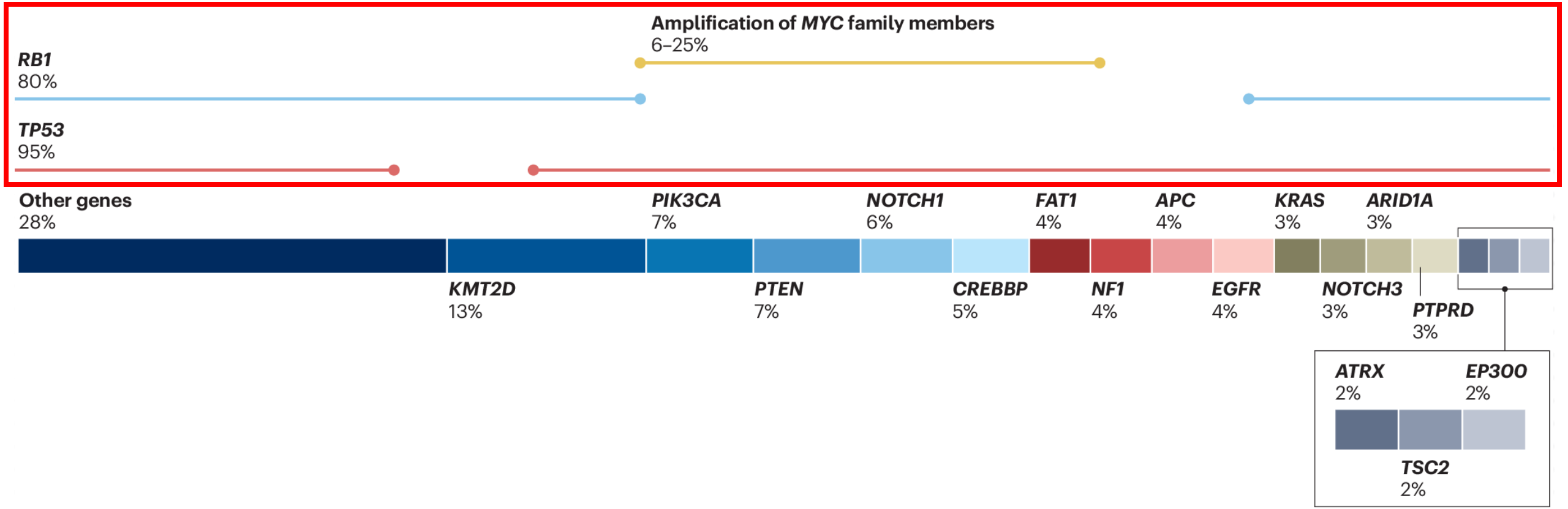
- A phase 3 study to compare the efficacy and safety of HS-20093 with standard-of-care chemotherapy in patients with relapsed SCLC (NCT06498479).
- A phase 3 study of HS-20093 versus active surveillance as consolidation therapy after chemoradiotherapy in subjects with limited-stage SCLC (NCT06526624).
- A Phase 1 clinical study to evaluate the safety, tolerability, pharmacokinetics, and clinical activity of GSK5764227 in participants with advanced solid tumors (NCT06551142).

OVERVIEW

Small Cell Lung Cancer

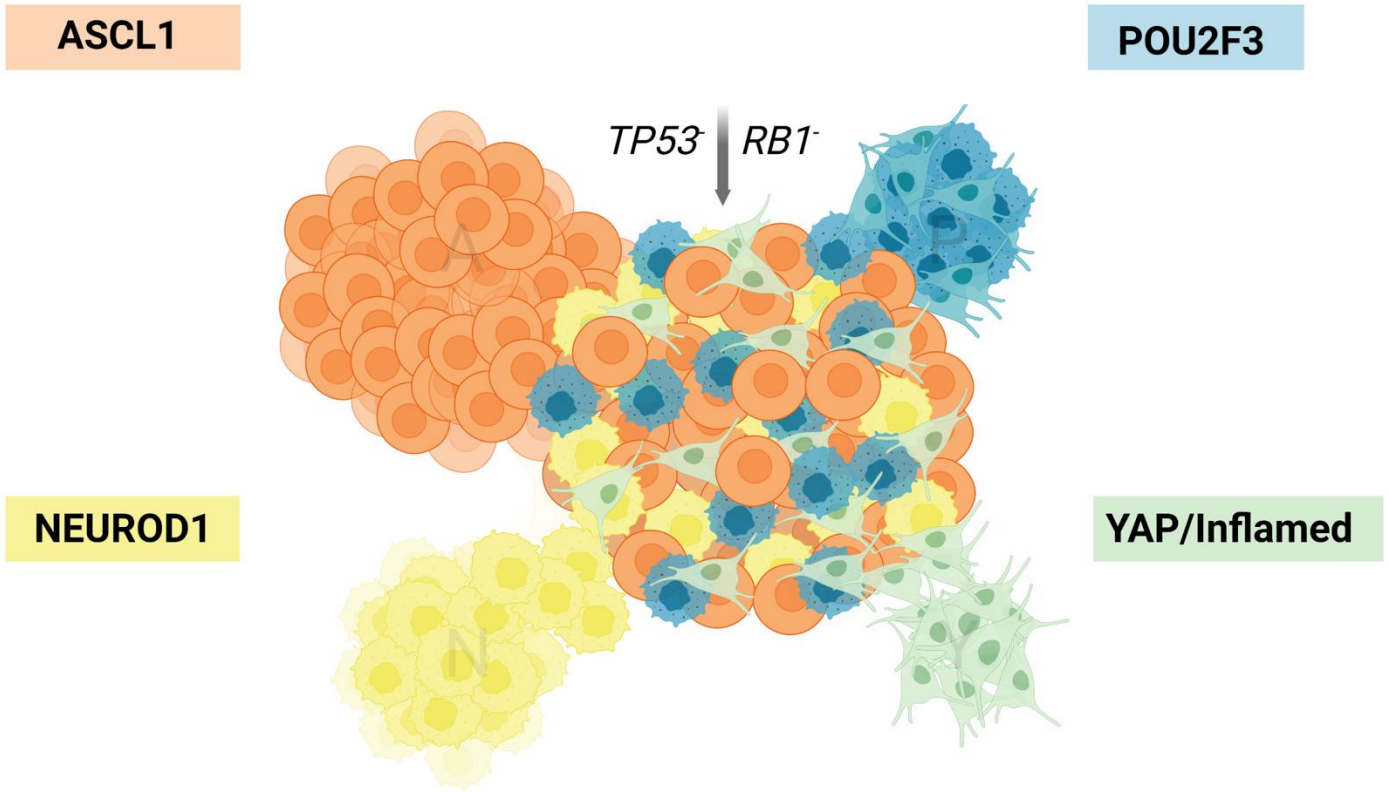
- Recent Advancements in Treatment
  - Limited-Stage
  - Extensive-Stage
- Emerging Trials & Novel Targets
- Biology & Biomarkers in SCLC

SCLC genetics:
major genomic aberrations; LOF mutations



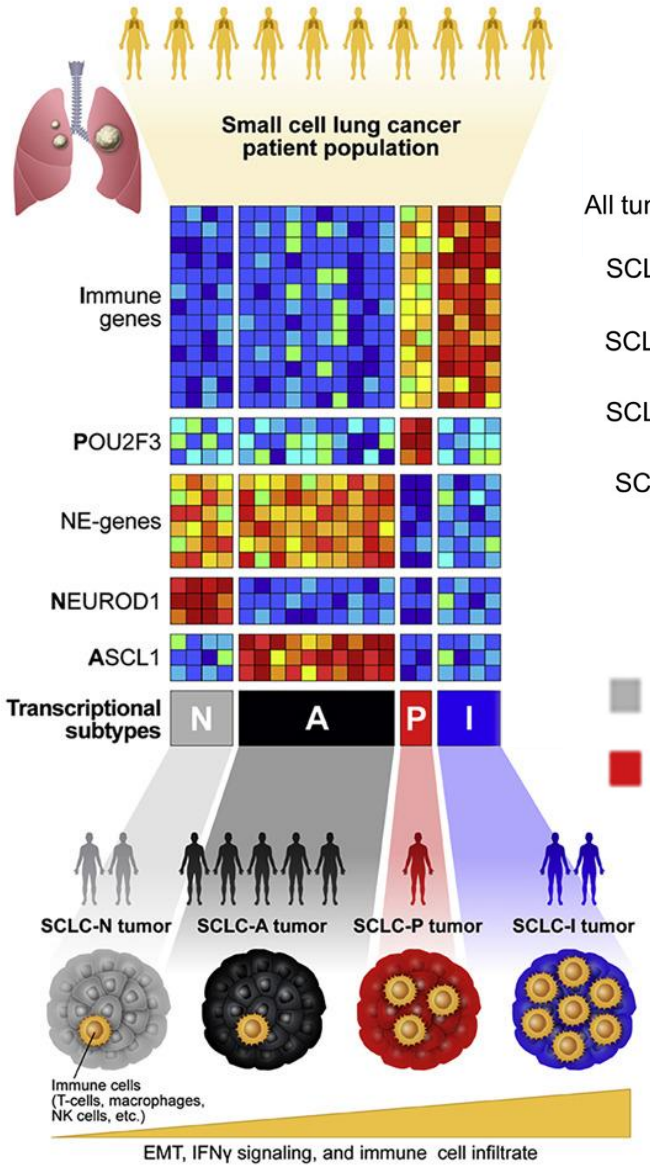
Sen T, et al., Nature Reviews Clinical Oncology, 2024

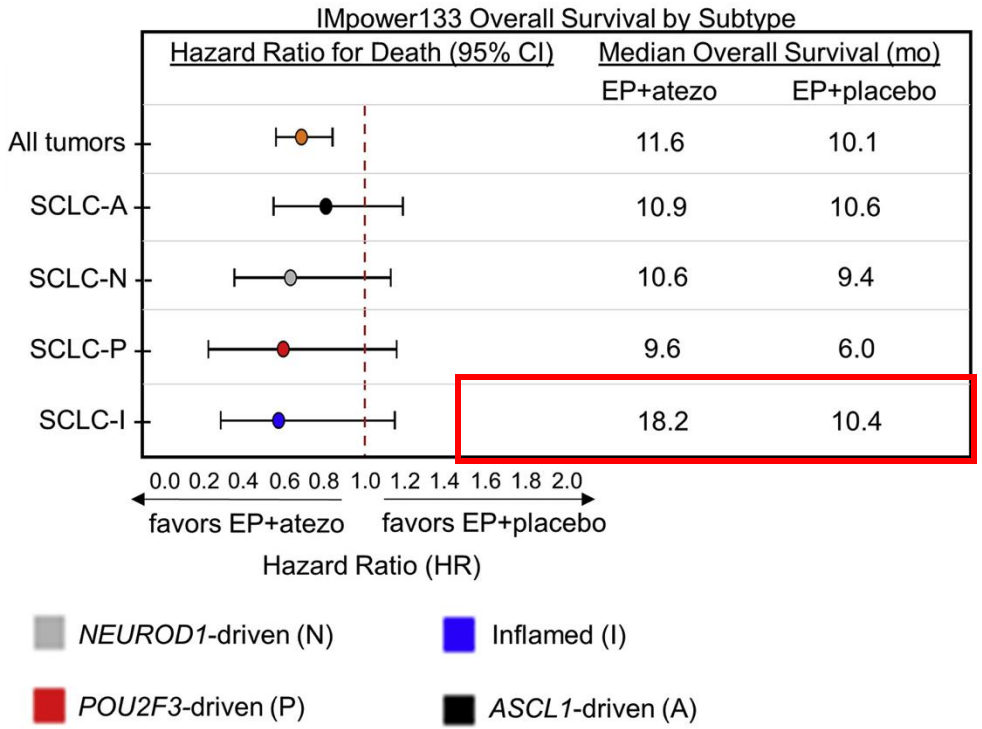
Biological significance of SCLC subtypes



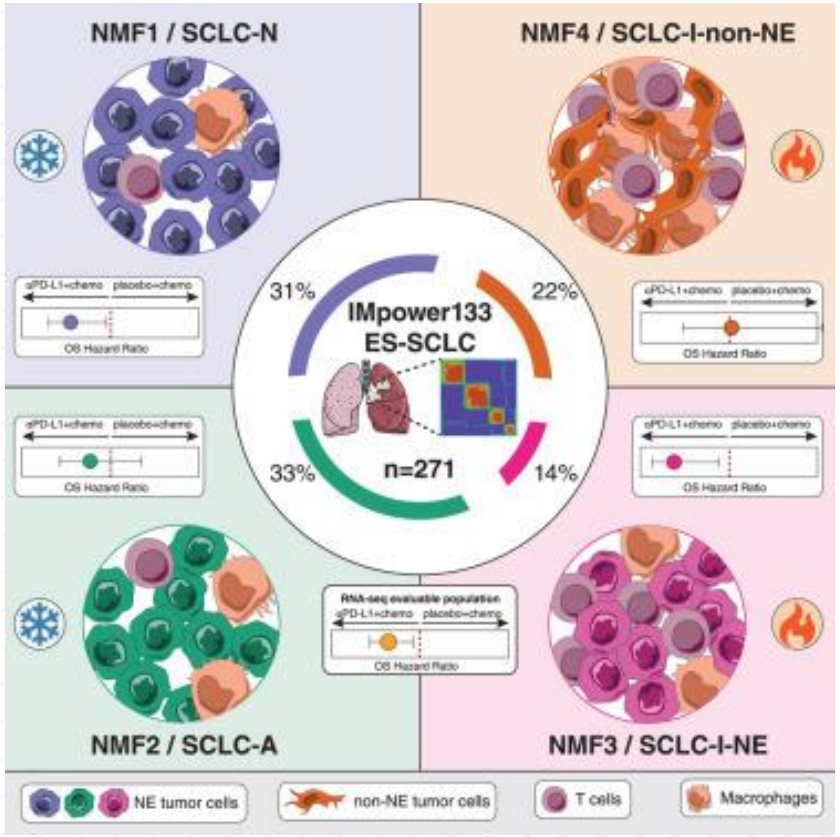
Modified from Sen T, et al., Nature Reviews Clinical Oncology, 2024

SCLC Inflamed subtype (SCLC I) may predict **differential** immunotherapy response





Gay et al, Cancer Cell, 2021



Nabet et al, Cancer Cell, 2024

Profiling of CM032 cohort reveals unanticipated promise (CD8/MHC-I as a biomarker)

ORIGINAL ARTICLE | SMALL CELL LUNG CANCER | VOLUME 18, ISSUE 9, P1222-1232, SEPTEMBER 2023

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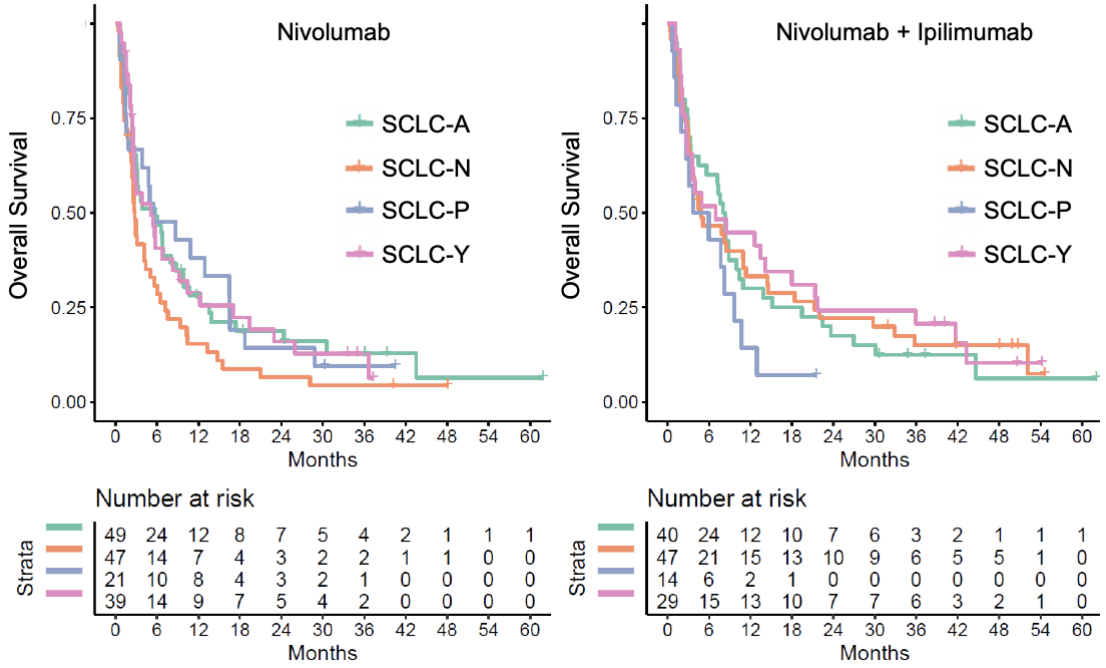
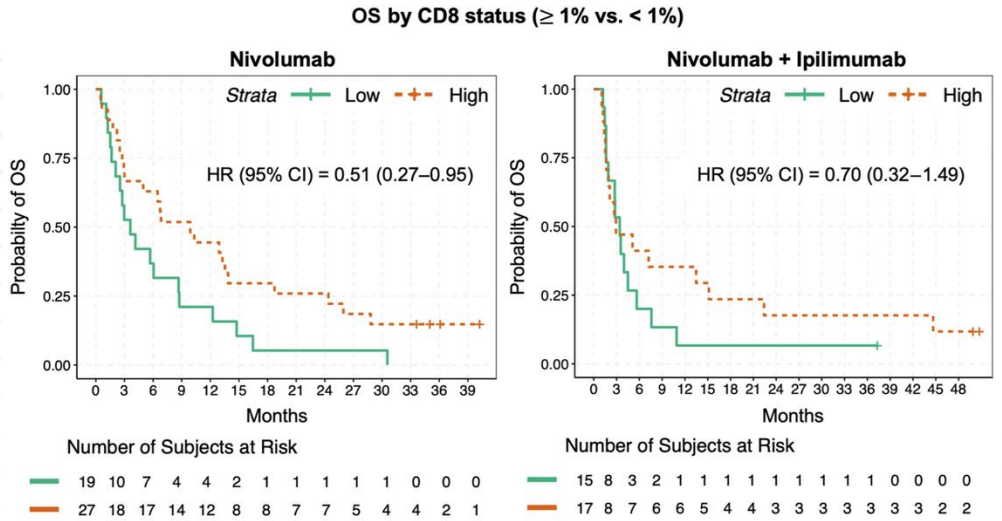
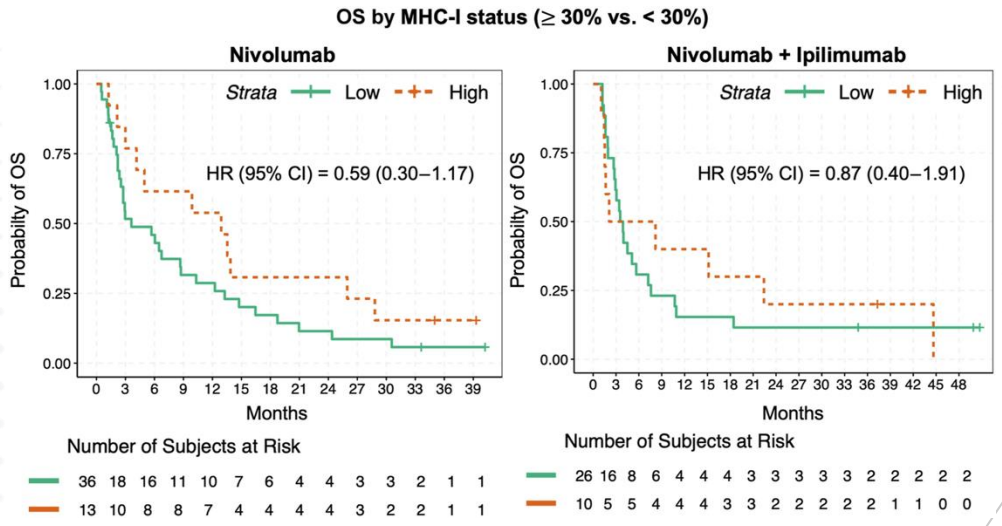
Clinical Benefit From Immunotherapy in Patients With SCLC Is Associated With Tumor Capacity for Antigen Presentation

Charles M. Rudin, MD, PhD • David Balli, PhD • W. Victoria Lai, MD • Allison L. Richards, PhD • Evelyn Nguyen, BA • Jacklynn V. Egger, BS • Noura J. Choudhury, MD • Triparna Sen, PhD • Andrew Chow, MD, PhD • John T. Poirier, PhD • William J. Geese, PhD • Matthew D. Hellmann, MD • Ann Forslund, PhD • Show less

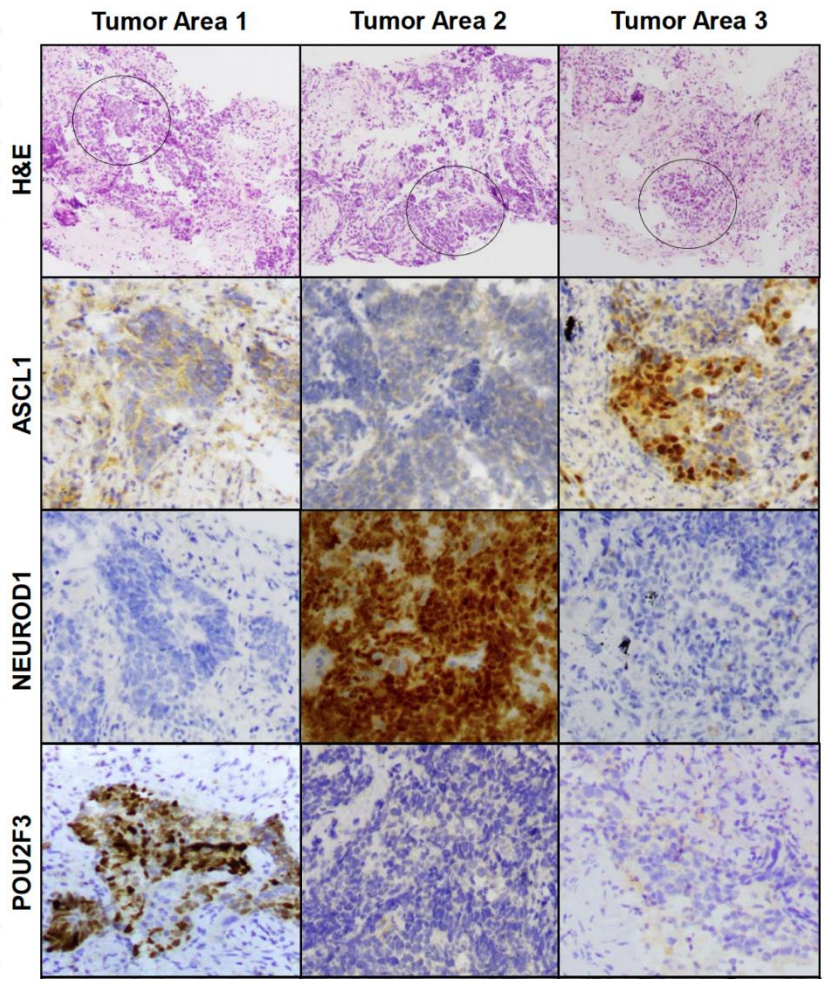
Published: May 17, 2023 • DOI: https://doi.org/10.1016/j.jtho.2023.05.008 • Check for updates







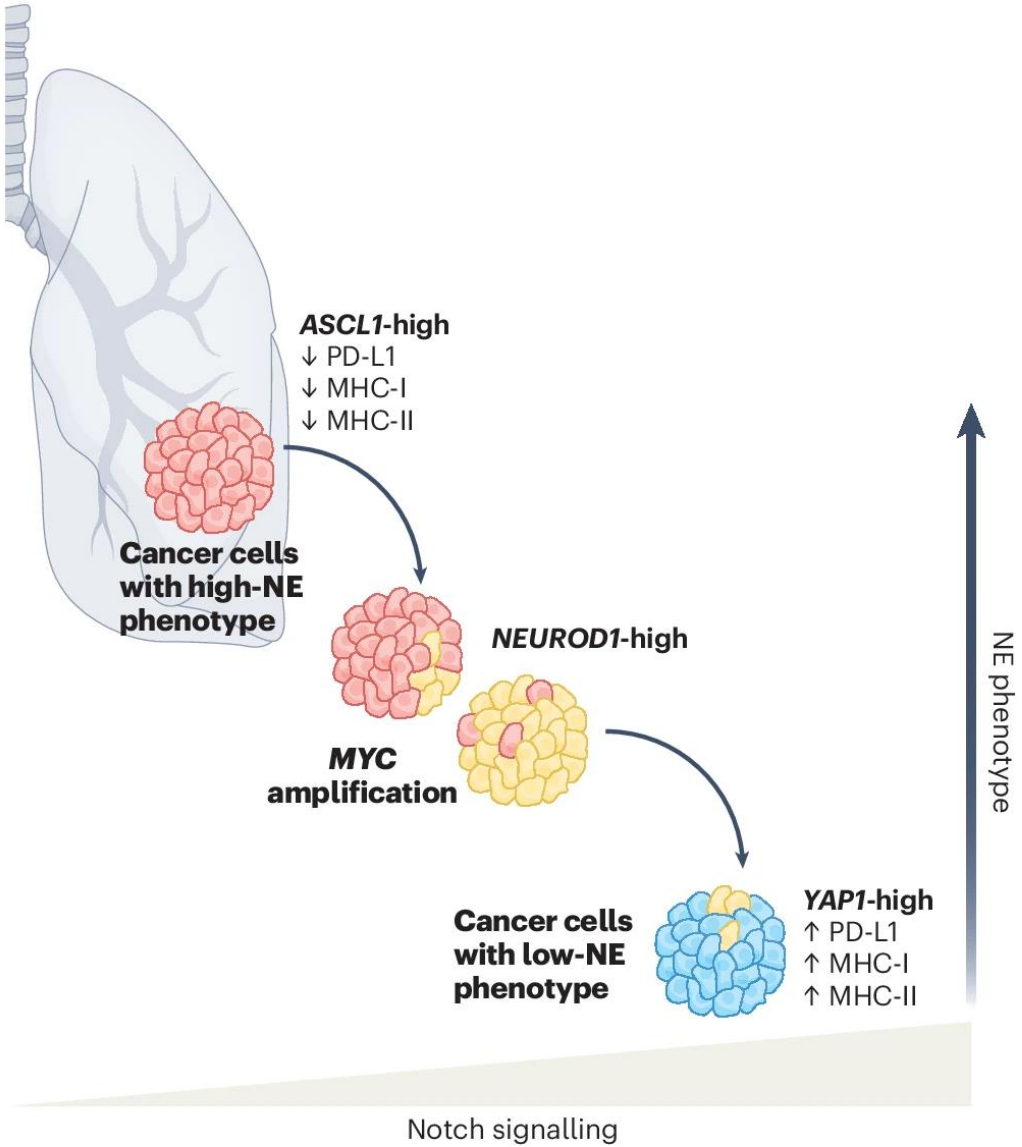
SCLC subtypes are heterogeneous and plastic



Baine et al., JTO 2020

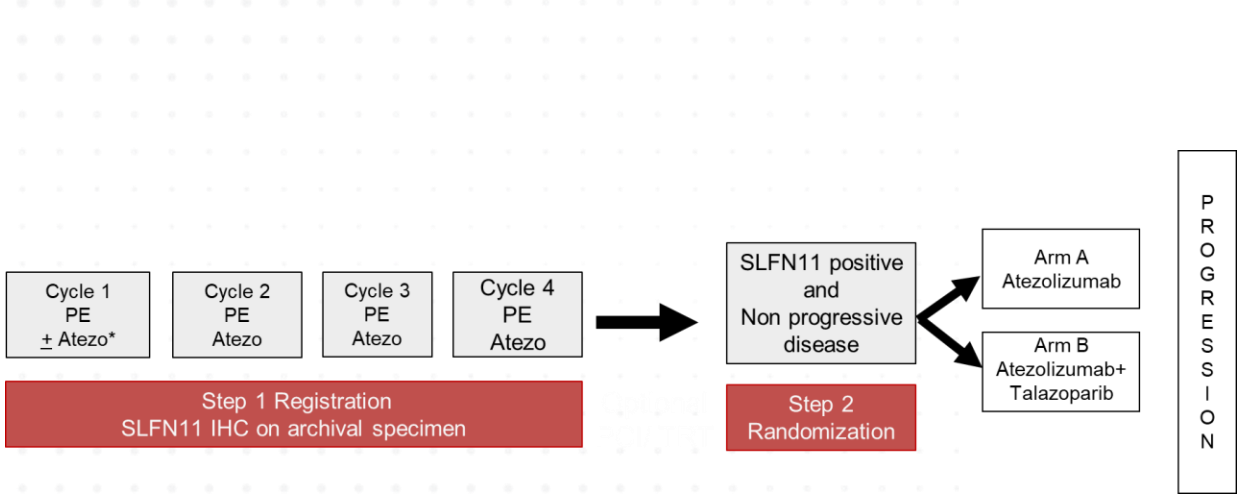
174 SCLC cases

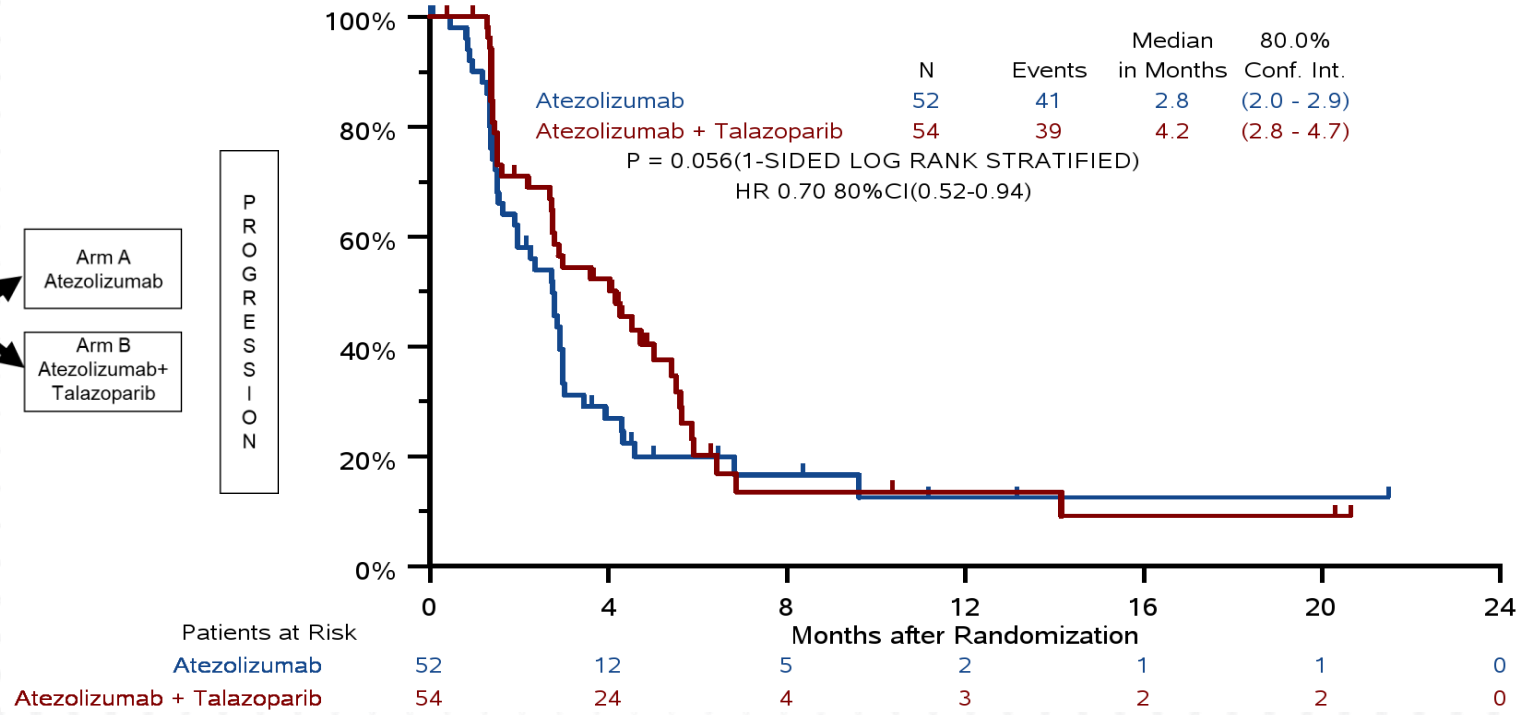
- Expression more heterogeneous in models
  - High prevalence of ASCL1/NEUROD1 co-expression



Sen et al., Nature Reviews Clinical Oncology, 2024

S1929: Phase II Study of Maintenance Atezolizumab Versus Atezolizumab in Combination with Talazoparib in Patients with SLFN11 Positive Extensive Stage Small Cell Lung Cancer (ES-SCLC) NCT04334941

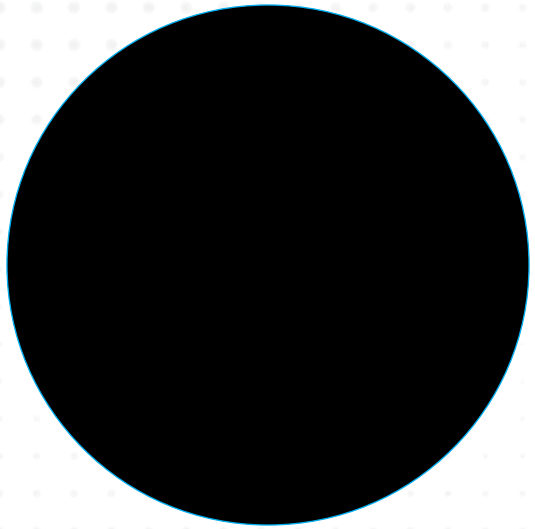


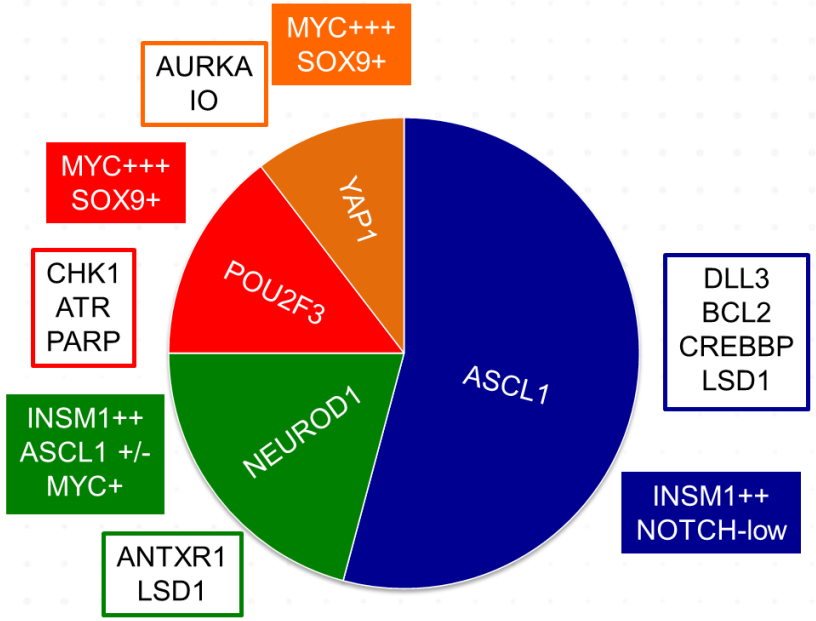


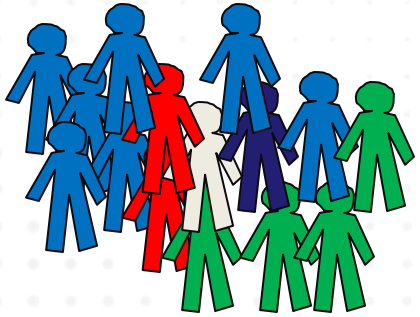
Maintenance Atezo+Tal improved PFS in SLFN11-positive patients with ES-SCLC.

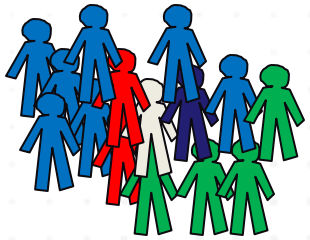
Karim et al., JTO, 2024

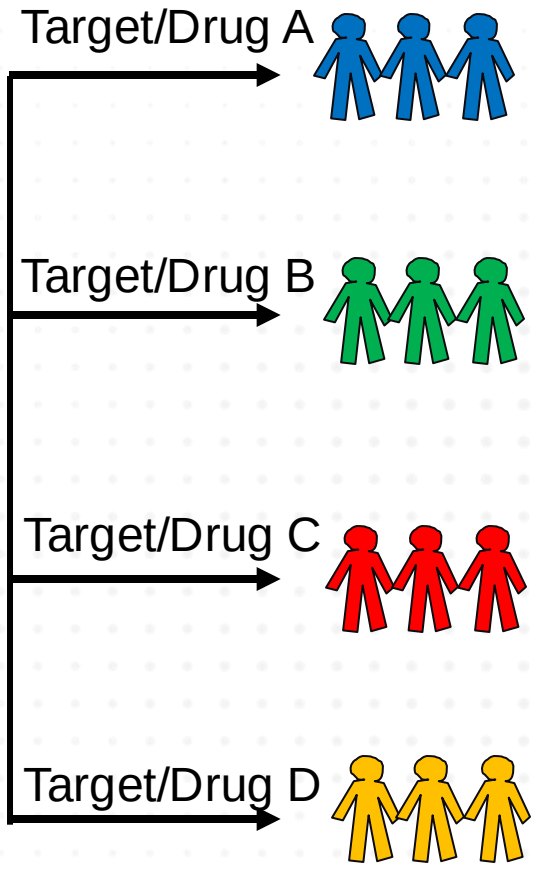
Evolving landscape of biomarkers in SCLC











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

THE SEN LAB

Step 1: Screening
N=838

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

Primary Endpoints: PFS
Secondary Endpoints: OS, Frequency, Severity of Adverse Events

Step 2: Randomization
N=312

Subtypes A/N, SLFN11 pos or Subtype P → **IO + PARP inhibitor** / **IO**

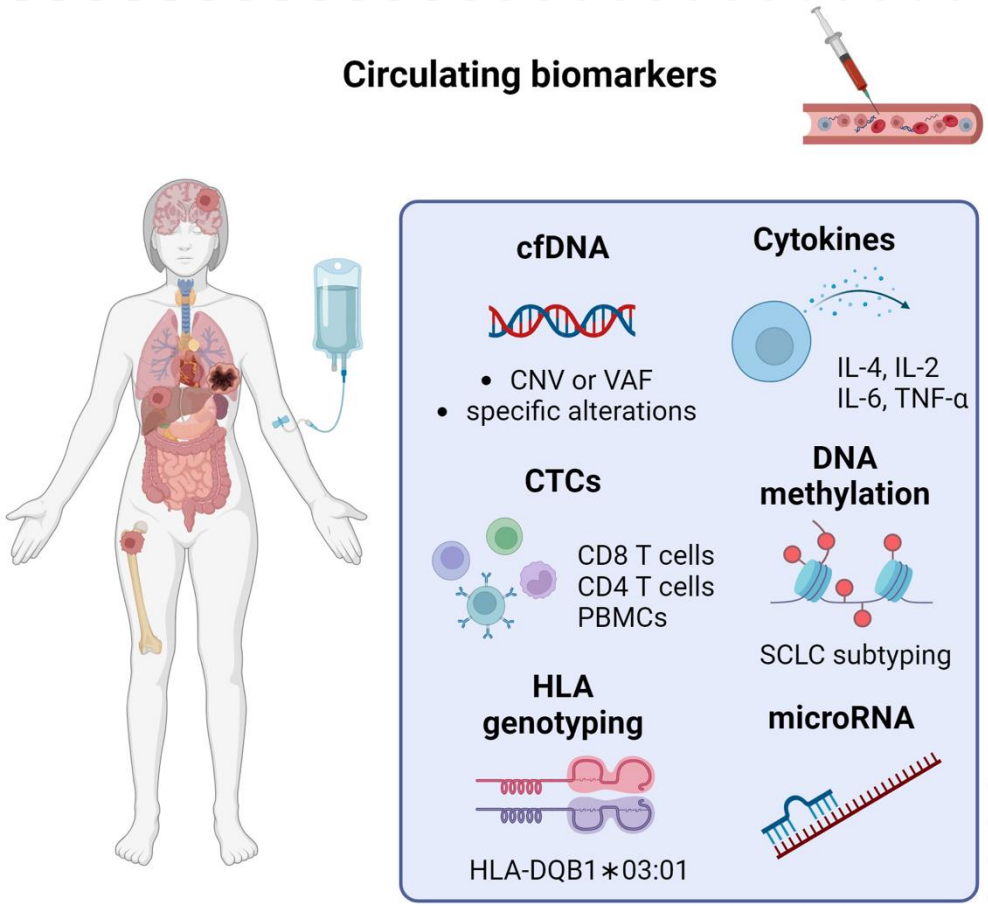
Subtypes A/N, SLFN11 neg → **IO + ATR inhibitor** / **IO**

Subtype I → **IO + NK activator** / **IO**

Protocol in Development

Study Chair: A. Chiang
Slide Courtesy- A. Chiang

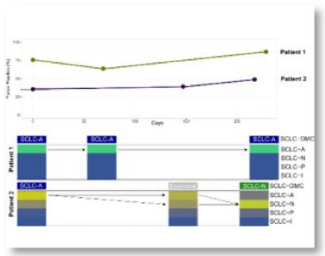
Liquid biopsy- a promising tool for tracking SCLC evolution and heterogeneity after therapy



Lorenzi et al., Front. Immunol., 2024

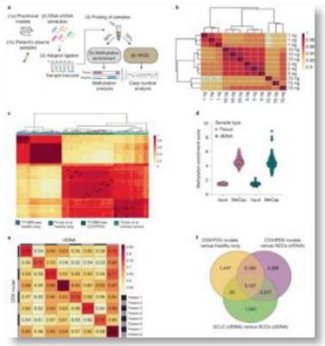
DNA Methylation

cfRRBS



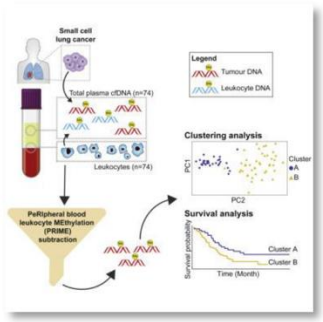
Heeke et al. WCLC 2022.

T7-MBD-seq



Chemi et al. Nat Cancer 2022.

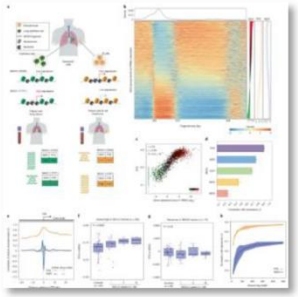
cfMeDip-seq



Ul-Haq et al. iScience 2022.

Fragmentomics

EPIC-seq



Esfahani et al. Nat Biotech 2022.

DELFI

Mathios et al. Nat Comms 2021.

Conclusions and Next Steps

THE SEN LAB

- There is a cohort of SCLC patients, small but real, who have durable benefit from immunotherapy
  - Strategies to improve the response to immunotherapy
  - Defining determinants of durable benefit

Acknowledgments

Twitter: @triparnasen
Email: triparna.sen@mssm.edu
Website:
https://labs.icahn.mssm.edu/senlab/home/

Patients and their families!