



Multidisciplinary Approaches to Cancer Symposium

What's New in Small Cell Lung Cancer?

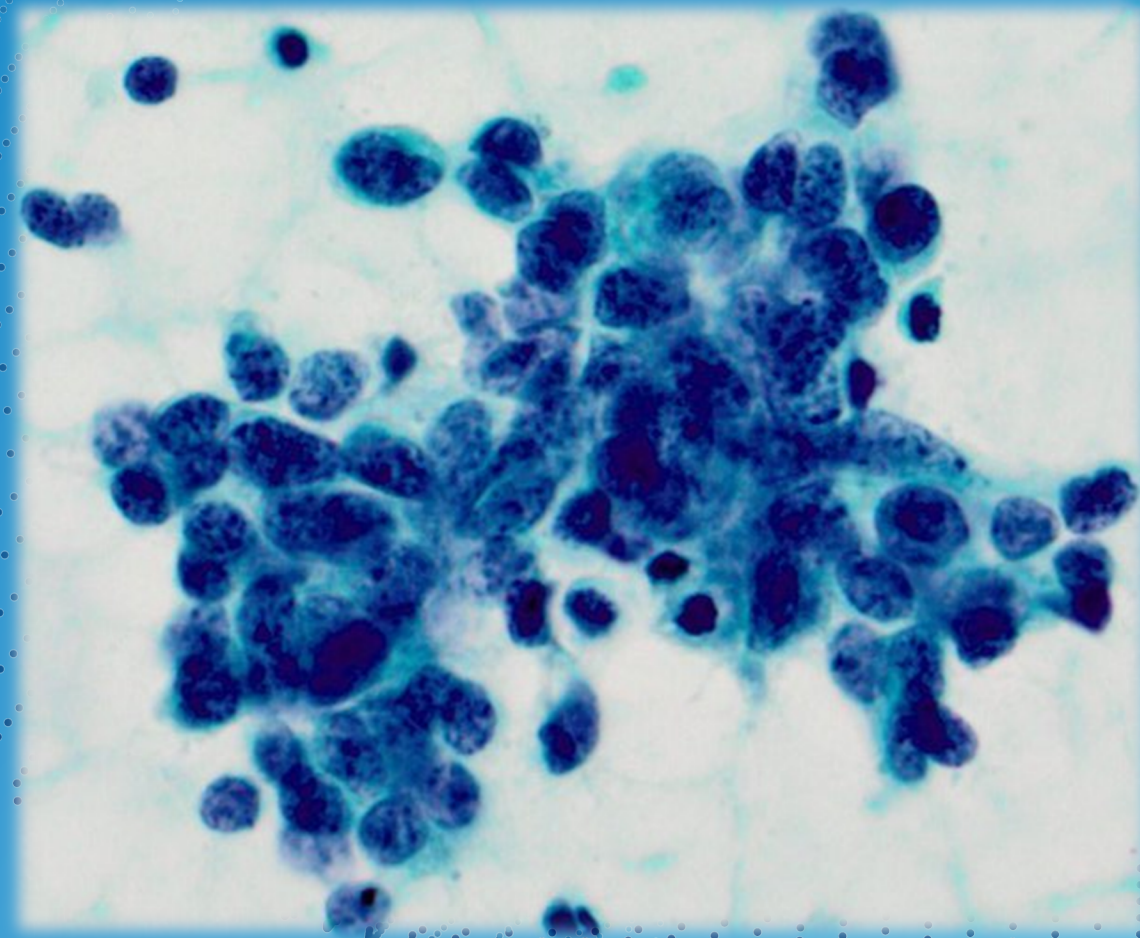
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City of Hope Comprehensive Cancer Center



Malignant SCLC from the bronchial brushings of a 60 yo male
McCormack M. [Case Study, Radiopaedia.org](https://www.radiopaedia.org/case-study/malignant-small-cell-lung-cancer-from-bronchial-brushings)

October 1, 2026

Disclosures

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

I have the following relevant financial relationships to disclose: (for the past 24 months)

- Employee of: N/A
- Consultant for: AbbVie, Amgen, AnHeart, Astra Zeneca, Black Diamond, BMS, Boehringer Ingelheim, Daiichi Sankyo, Exact, Foresight, Foundation Medicine, Guardant, Genentech, Gilead, Guardant, Immunity Bio, Jazz, JNJ, Merck, Nuvalent, Nuvation, Onvivo, Pfizer, Regeneron, Summit, Takeda, Taiho, Tempus
- Speaker's Bureau for: N/A
- Stockholder in: N/A
- Honoraria from: AbbVie, Amgen, AnHeart, Astra Zeneca, Black Diamond, BMS, Boehringer Ingelheim, Daiichi Sankyo, Exact, Foresight, Foundation Medicine, Guardant, Genentech, Gilead, Guardant, Immunity Bio, Jazz, JNJ, Merck, Nuvalent, Nuvation, Onvivo, Pfizer, Regeneron, Summit, Takeda, Taiho, Tempus
- I served as DSMB chair for a Janssen study, uncompensated.



Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

This presentation is dedicated solely to research or other issues that do not contain a direct patient care component.



Discussion Agenda

1. Standard of care and current treatment landscape

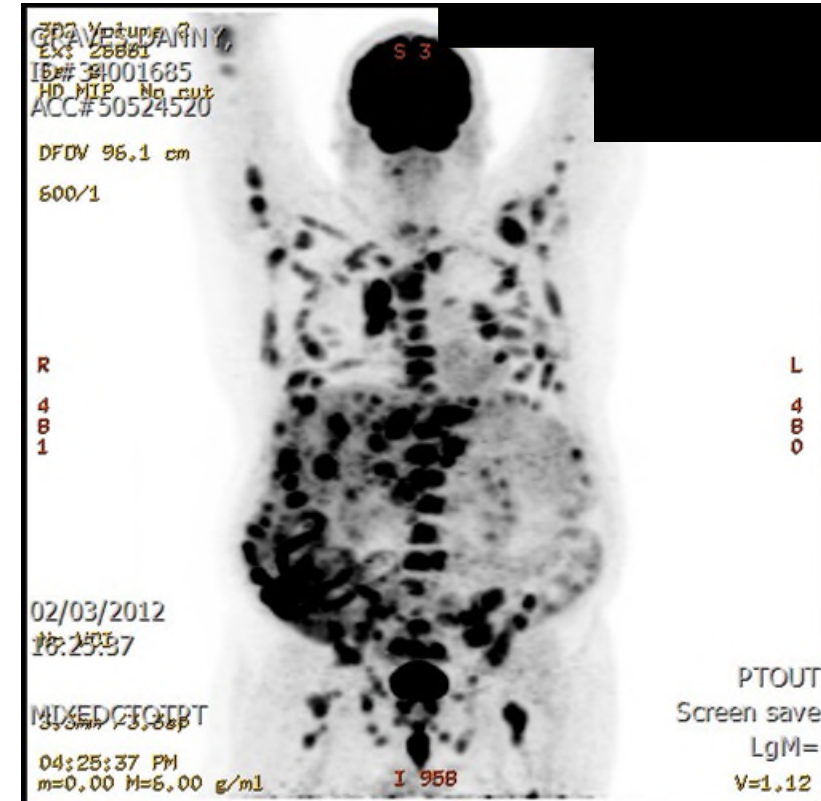
- Key markers of recent progress in treating SCLC
- Immune Checkpoint Inhibitors (ICIs) in SC-SCLC and ES-SCLC

2. Novel agents based on a growing understanding of SCLC biology

- Bispecific T-cell Engagers (BiTEs)
- Antibody Drug Conjugates (ADCs)
- Unmet space for treatment of transformed SCLC (T-SCLC)
- CAR T, PROTAC, and beyond

There is nothing “small” about small cell

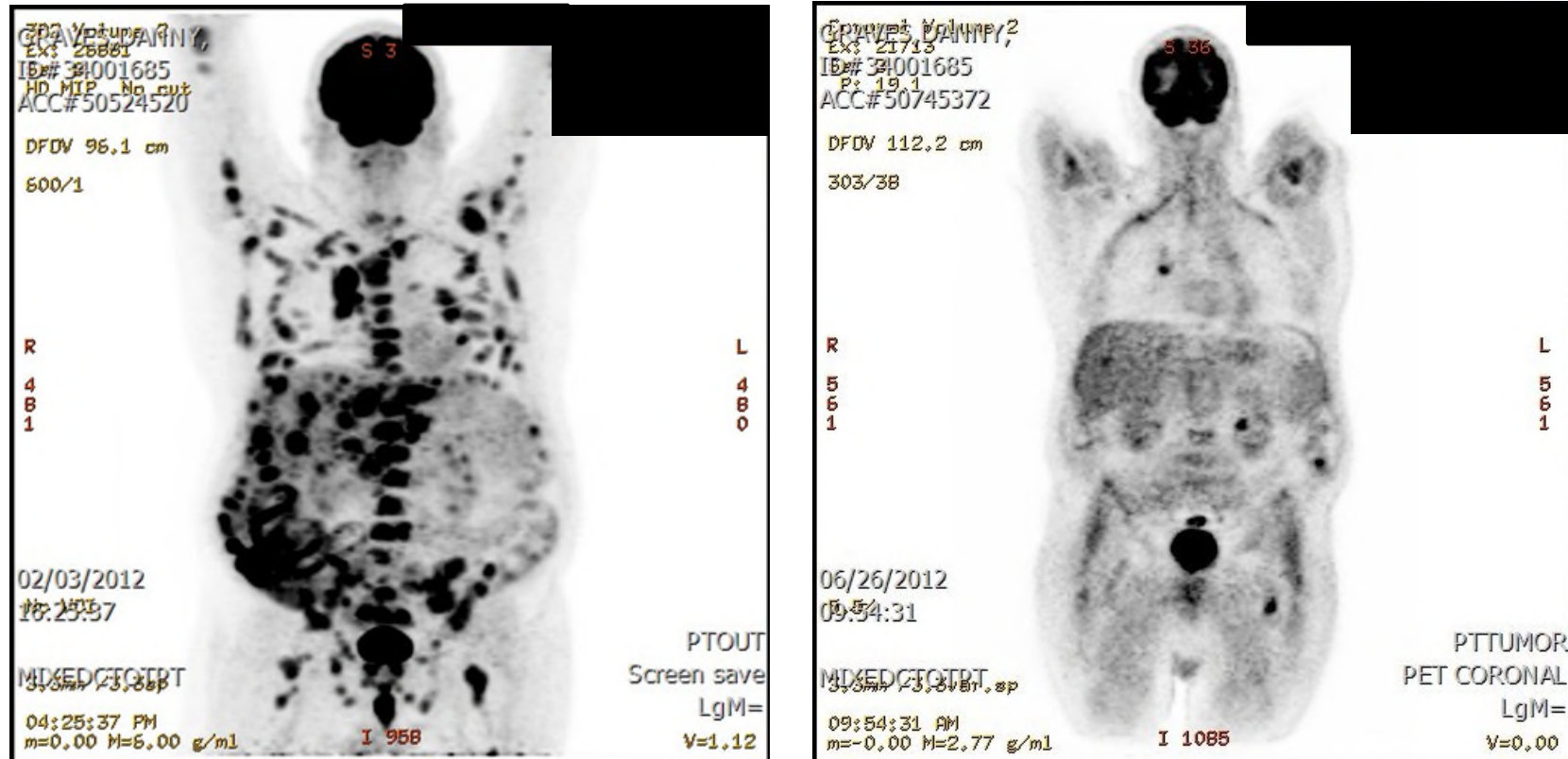
- Small cell lung cancer (SCLC) is an aggressive form of lung cancer of the neuroendocrine lineage
- SCLC's ability to evolve and rapidly adapt can lead to the development of resistance to therapies and relapse
- For decades, most patients would succumb to the disease within 12 months from diagnosis
- Breakthroughs are desperately needed for patients diagnosed with SCLC



Recalcitrant Cancer Research Act of 2012.
Rossi, A. J Thorac Dis, 2016.
Huang, et al. Thorac Canc. 2021.
NCI Scientific Framework for SCLC, 2014.



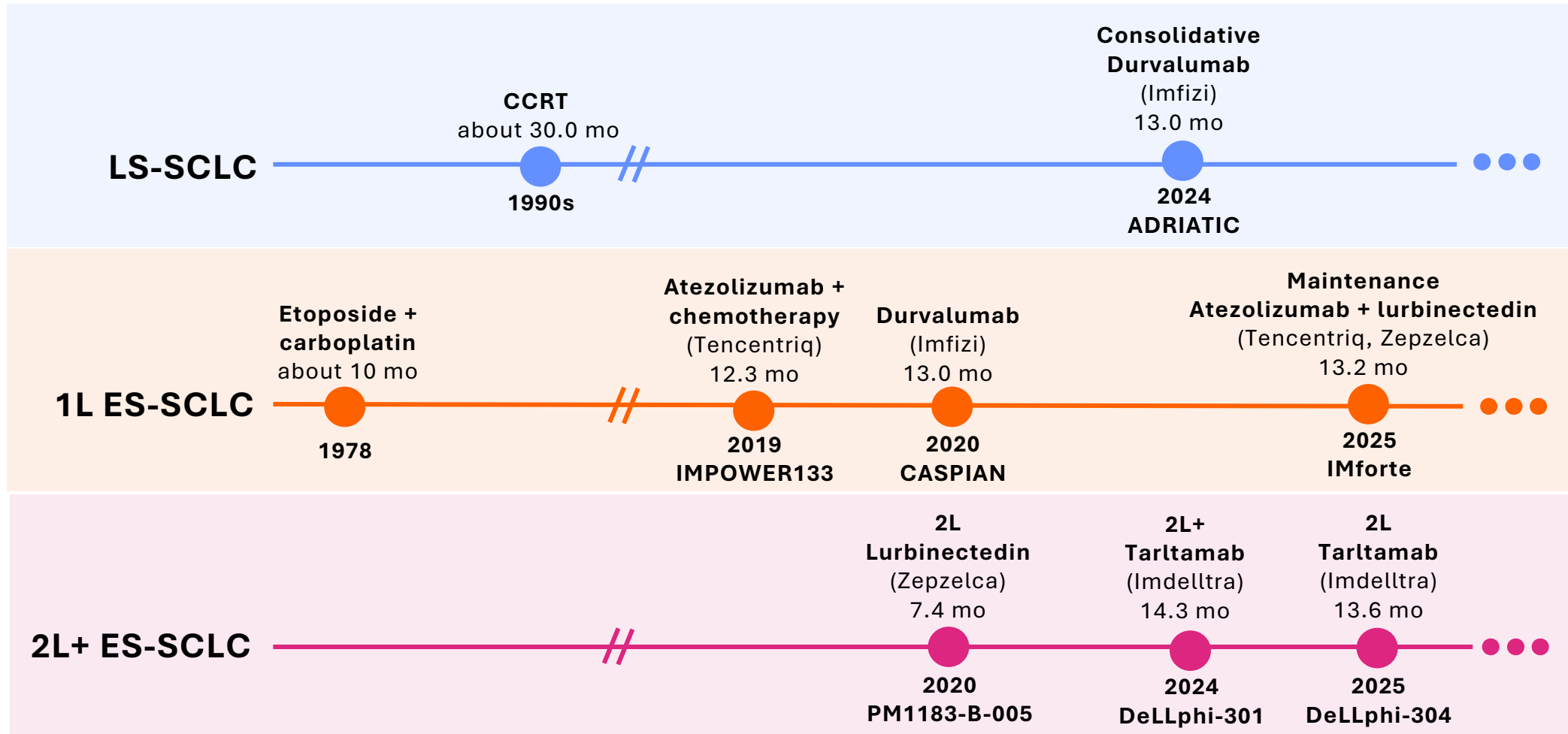
SCLC has an exceptional response to platinum/etoposide



...but progression is nearly inevitable.

What is going to move the needle for patients with SCLC?

Landmark FDA approvals for the treatment of SCLC



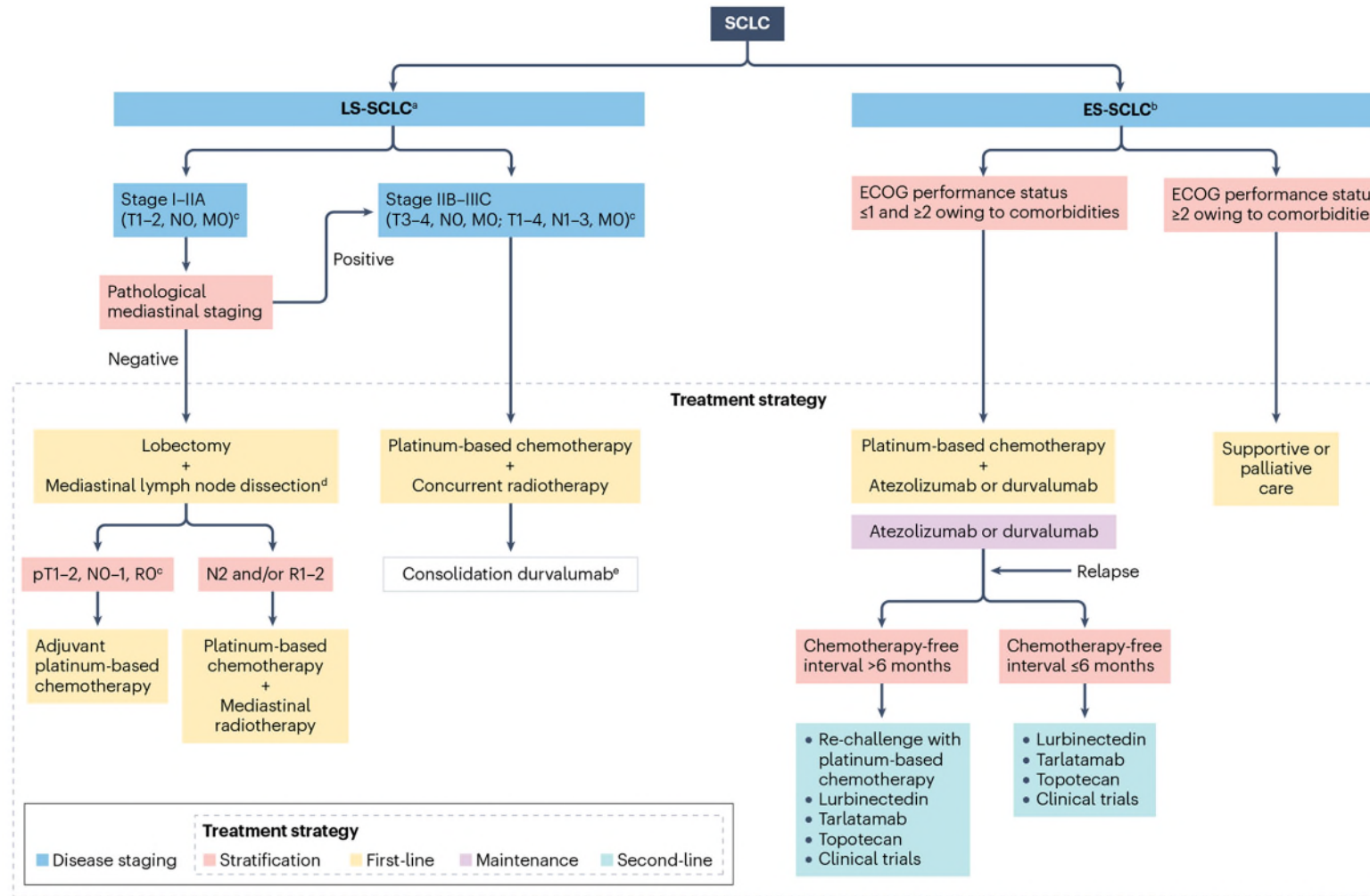
Adapted from:
Arya, Dyer, Hegi-Johnson, et al. *Am Soc Clin Oncol Educ Book*, 2026.
Curtis, Gordon, Pataillot-Meakin et al. *Drug Discovery Online*, 2025.



The current treatment landscape of SCLC

30-35% of patients have Limited-Stage (LS) SCLC

"Limited" to one hemothorax and can be safely encompassed in a single radiation field

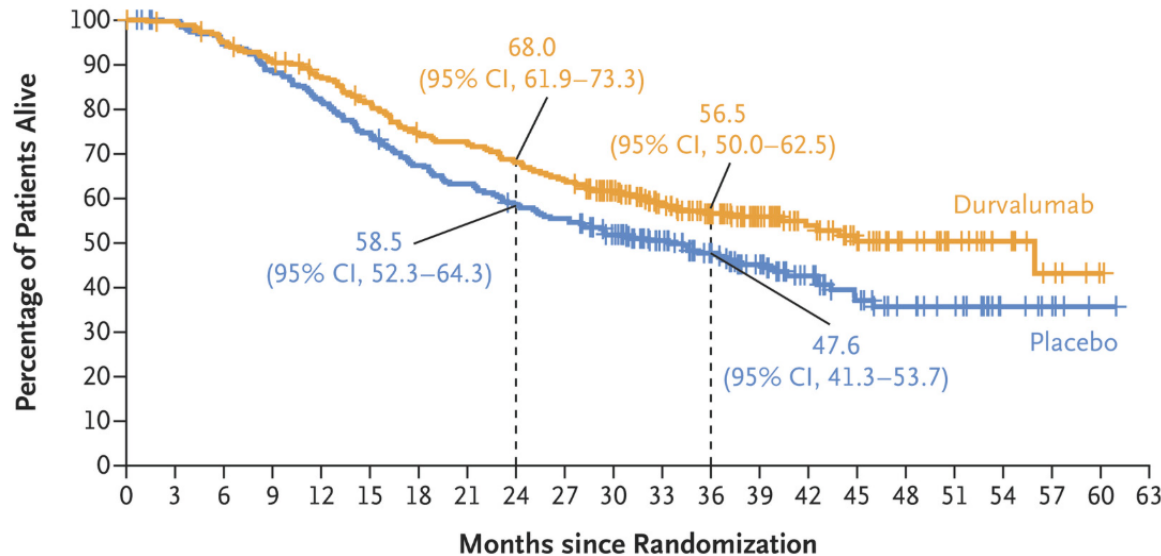


65-70% of patients have Extensive-Stage (ES) SCLC

ADRIATIC (2024): Consolidative durvalumab post-CCRT improved OS in LS-SCLC

- Trial regime was well tolerated with no significant increase in grade 3/4 pneumonitis
- FDA approval in 2024 and implementation into national guidelines advanced immunotherapy into LS-SCLC

A Overall Survival



	No. of Deaths/ Total No. (%)	Median Overall Survival (95% CI) mo
Durvalumab	115/264 (43.6)	55.9 (37.3–NR)
Placebo	146/266 (54.9)	33.4 (25.5–39.9)
Stratified hazard ratio for death, 0.73 (98.321% CI, 0.54–0.98) P=0.01		

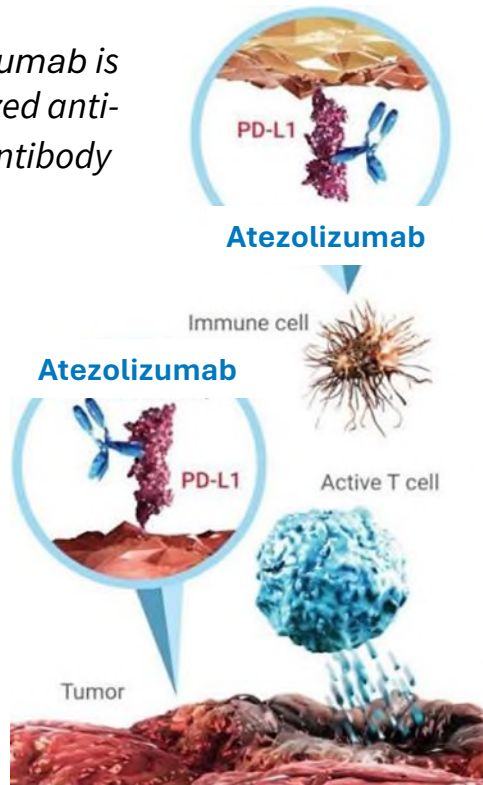
No. at Risk

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

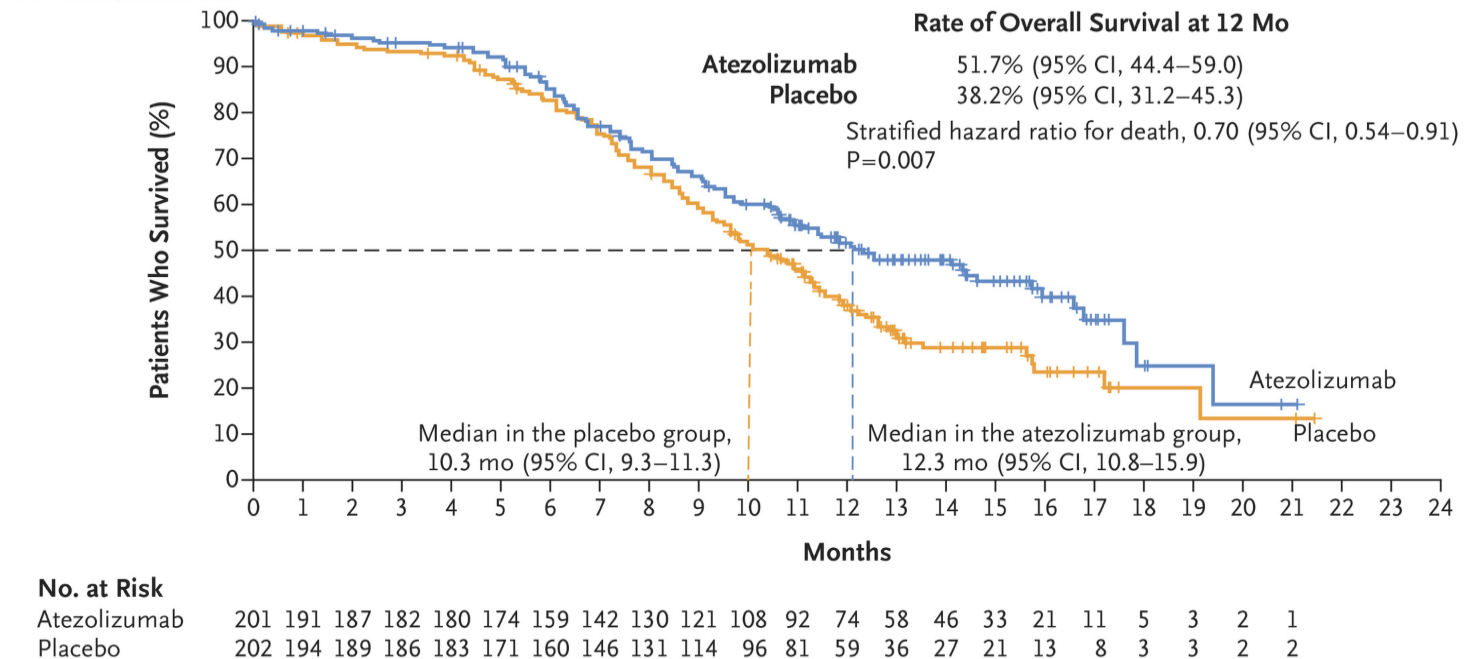


IMpower133 (2019): Atezolizumab added to carboplatin-etoposide extended OS in ES-SCLC

Atezolizumab is a humanized anti-PD-L1 antibody



A Overall Survival

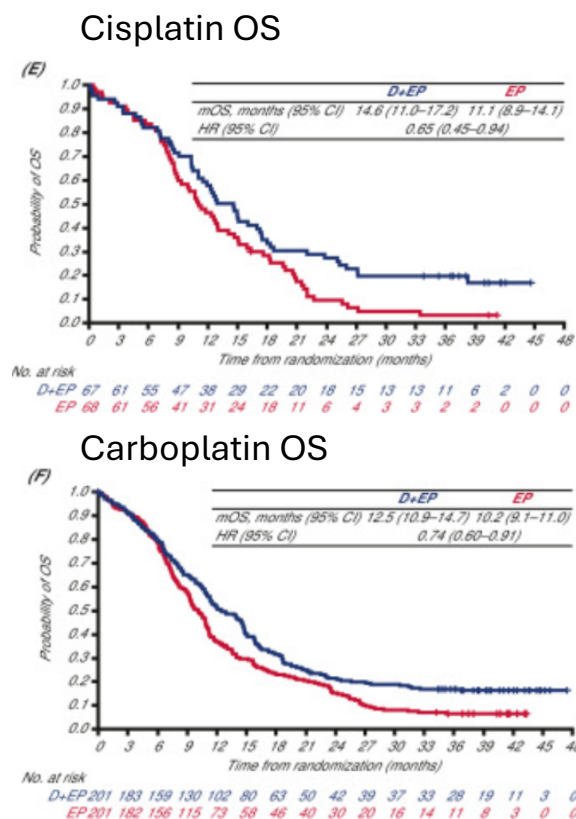


TECENTRIQ® (atezolizumab) proposed mechanism of action
Horn, Mansfield, Szczesna, et al. *N Engl J Med*, 2018.

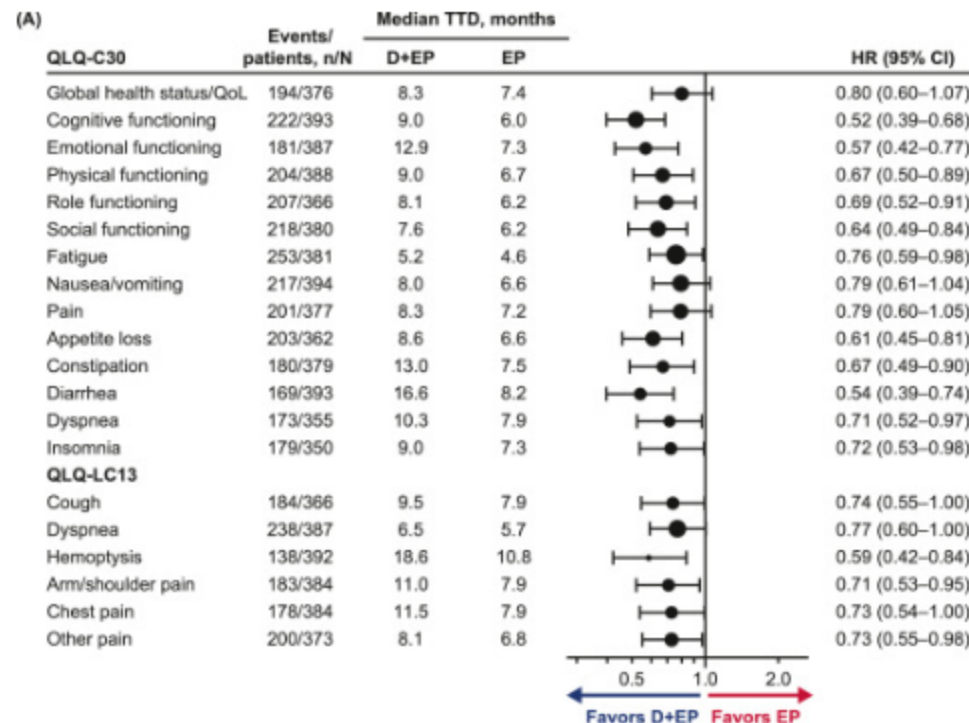


CASPIAN (2020): Durvalumab added to platinum-etoposide extended OS in ES-SCLC

Study allowed physicians to choose the type of platinum chemotherapy



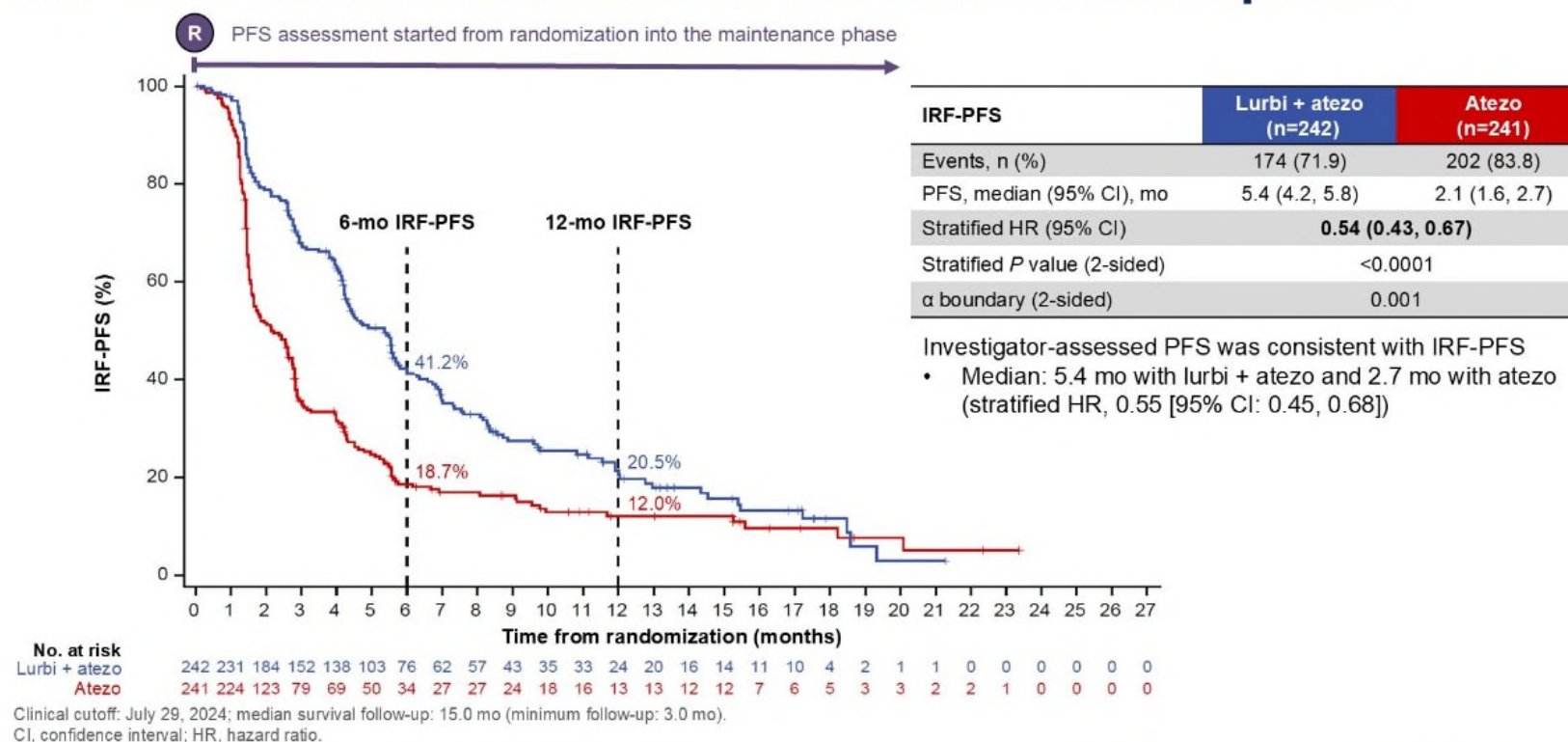
OS favored durvalumab plus EP vs. EP alone regardless of sex or platinum agent



IMforte (2025): Maintenance atezolizumab and lurbinectedin improved PFS vs. monotherapy (5.4 vs. 2.1 mo)

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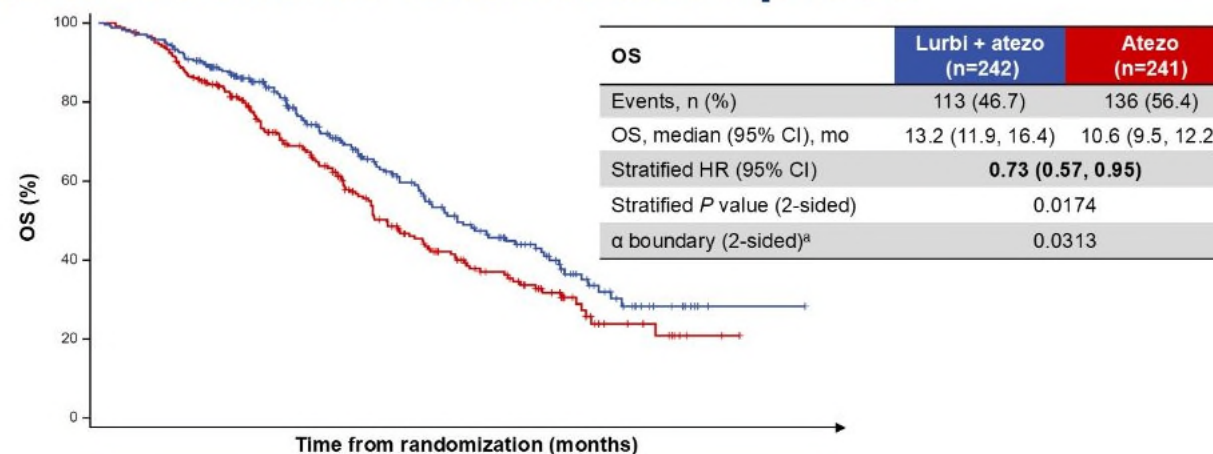
IRF-PFS from randomization into maintenance phase



IMforte (2025): Maintenance atezolizumab and lurbinectedin improved OS vs. monotherapy (13.2 vs. 10.6 mo)

12

OS from randomization into maintenance phase



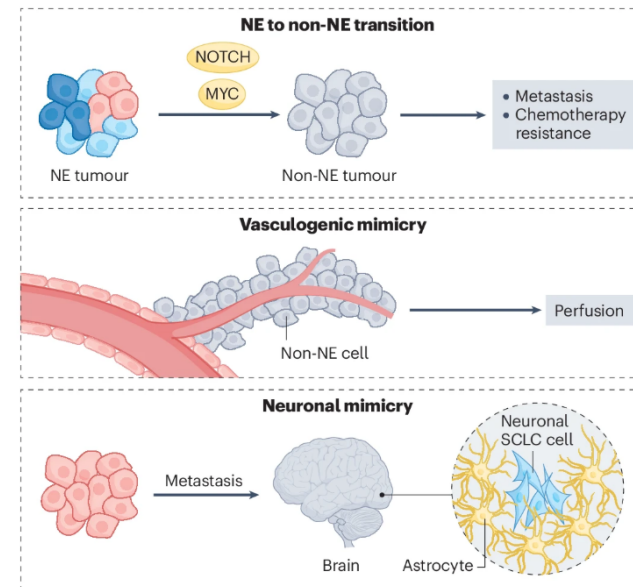
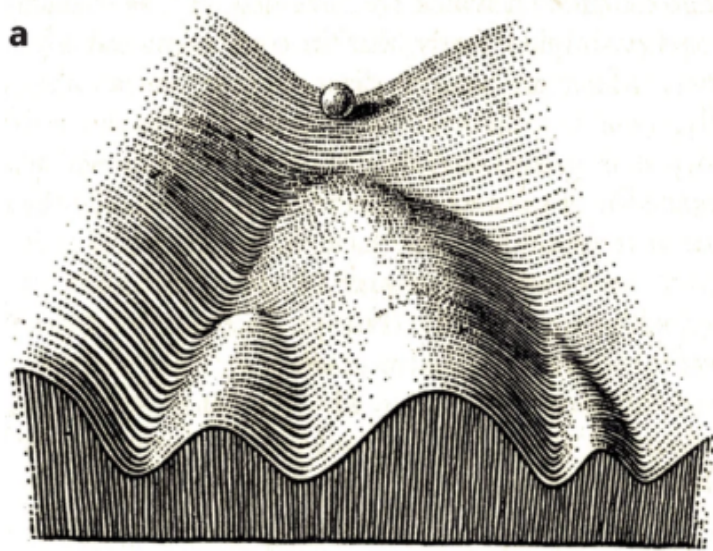
IMforte results do not include time on induction treatment

^a Median time from start of induction treatment to randomization was analyzed for 483 randomized patients. Note: 660 patients were enrolled into the induction phase, out of whom 177 patients were not randomized into the maintenance phase.



SCLC is heterogeneous and phenotypically plastic: How do you continue to treat aggressive adaptability?

- 2-years survival rates are still only 14 - 22% for SoC chemoimmunotherapy regimes
- Relapses occur within 6 months in nearly 50% of patients



SCLC needs more durable responses and treatments that target its biology.

Zugazagoitia & Paz-Ares, *J Clin Oncol*, 2022.
Khurshid, Ismaila, Bain, et al. *J Clin Oncol*, 2023.
Moris, Pina, Arias. *Nat Rev Genet*, 2026.
Simpson, Rothwell, Blackhall, et al. *Nat Rev Cancer*, 2025.



Can neuroendocrine (NE) subtyping help inform first line chemolO maintenance?

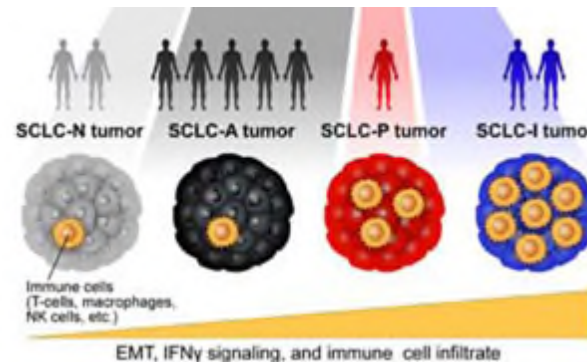
- SCLC has been defined into dominant neuroendocrine (NE) subtypes based on differential expression of transcription factors

NE-high subtypes:

- SCLC-N (*NEUROD1*)
- SCLC-A (*ASCL1*)

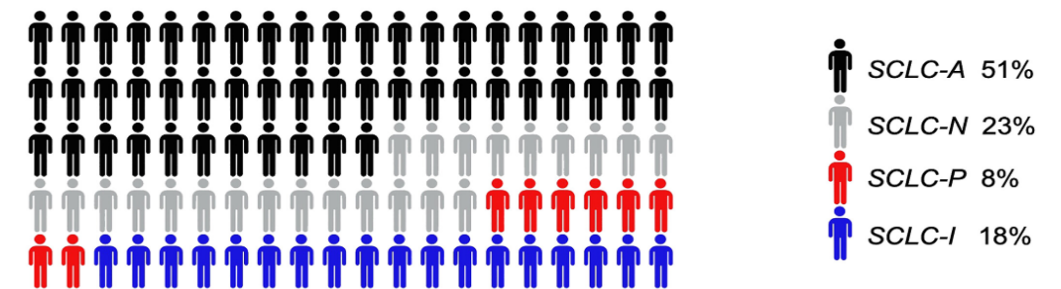
NE-low subtypes:

- SCLC-P (*POU2F3*)
- SCLC-I (Inflamed/*YAP1*)



Cay, Stewart, Park, et al. *Cancer Cell* (2022).

Neuroendocrine Subtype Distribution of Treatment-Naïve Extensive-Stage SCLC



Shields, Chiang, Byers. et al. *Cancer*, 2025.

But is not currently SoC to send SCLC tumor biopsy samples for clinical NGS.
So there is no clear way to translate these subtypes into effective therapies – yet.

PRISM: Using biomarker tests to select and test new, personalized treatments from ES-SCLC

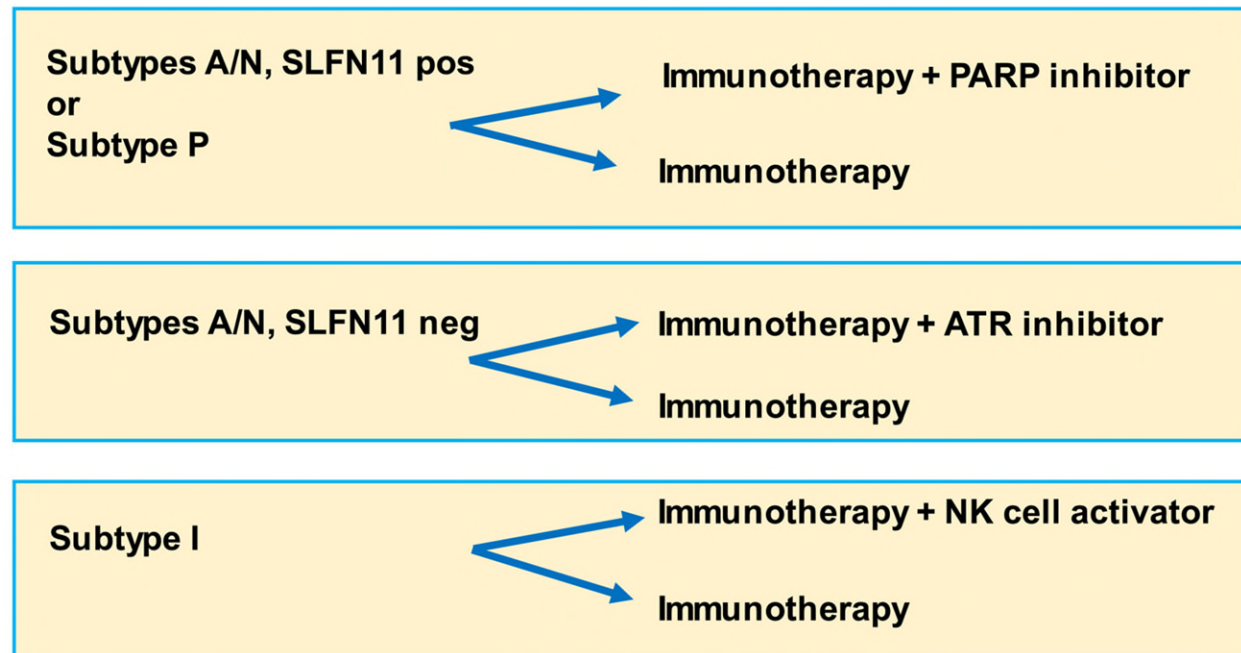
Step 1: Screening

- ES-SCLC Screening
- Tissue available for testing
- Asymptomatic or Stable Treated Brain Lesions

Primary Endpoints: PFS

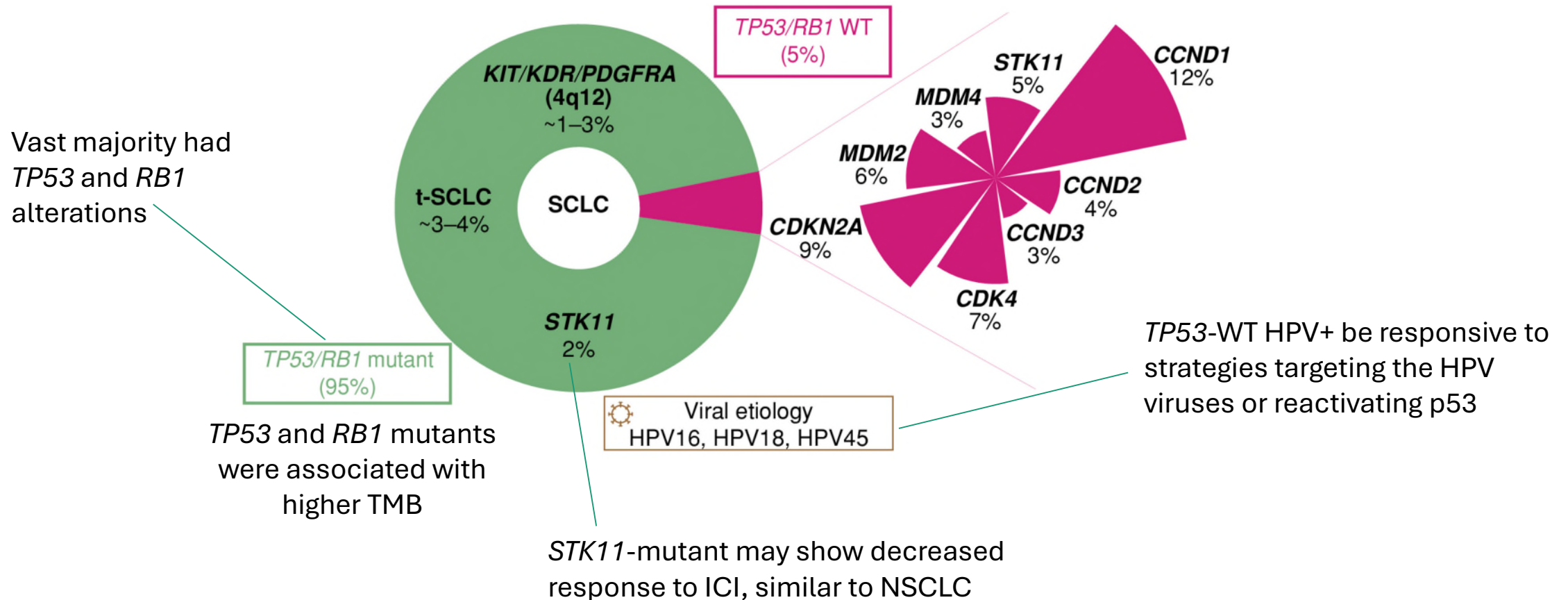
Secondary Endpoints: OS,
Frequency, Severity of Adverse
Events

Step 2: Randomization

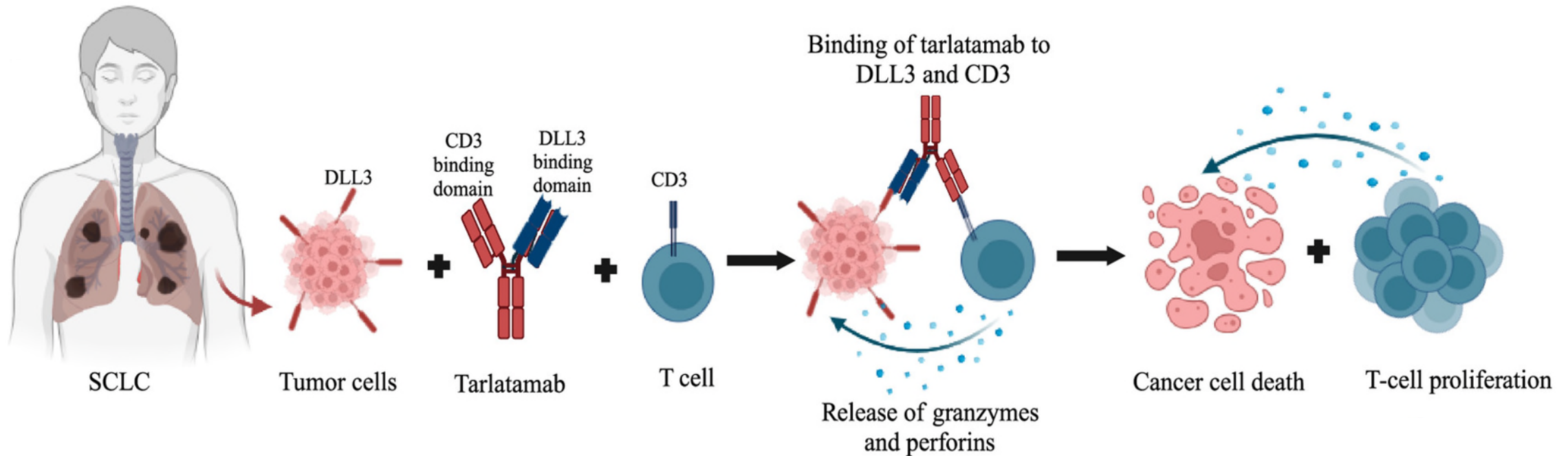


Mutational subtyping could help inform treatment strategies

Comprehensive genomic profiling of FFPE sections from 3600 SCLC patients



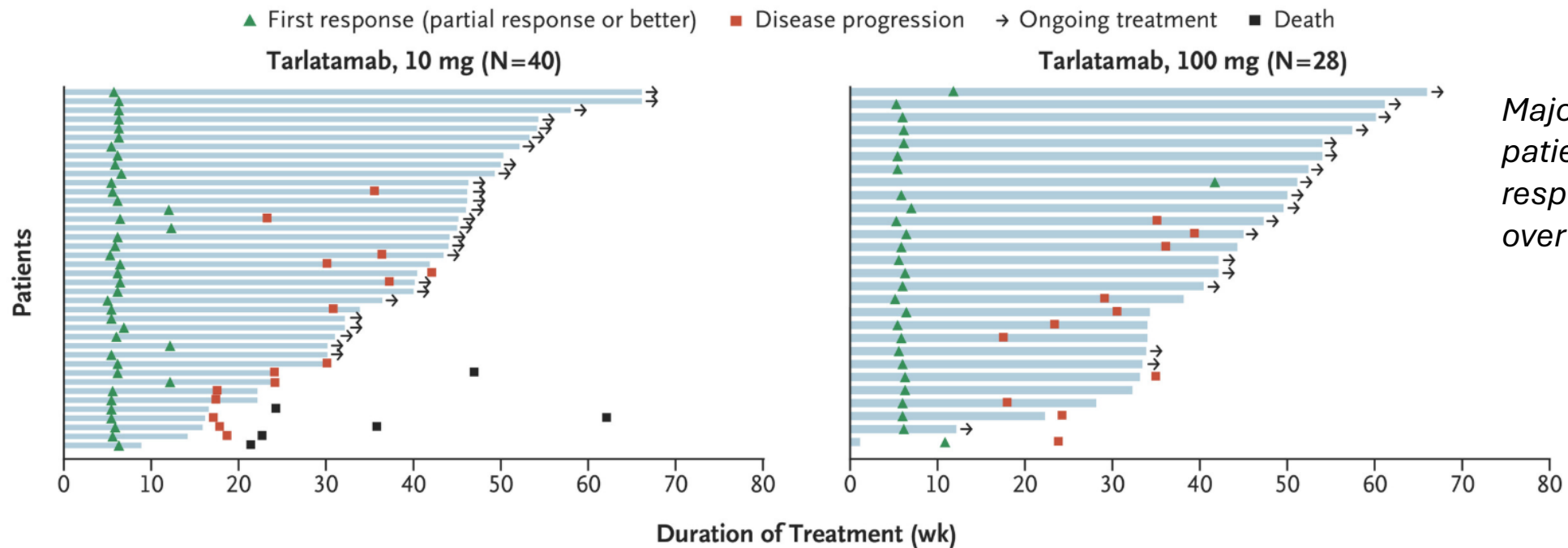
Tarlatamab and other Bispecific T-cell Engagers (BiTEs) target SCLC-specific surface markers like DLL3



➤ *Tarlatamab received FDA accelerated approval in May 2024 and full approval in Nov 2025*

DeLLphi-301 (2024): 2L tarlatamab showed antitumor activity with durable response in ES-SCLC

- ORRs of 40% (10 mg) and 32% (100 mg)



Majority of patients had responses lasting over 6 months!

DeLLphi-301 (2024): Tarlatamab introduce toxicities specific to BiTEs that differ from chemolO

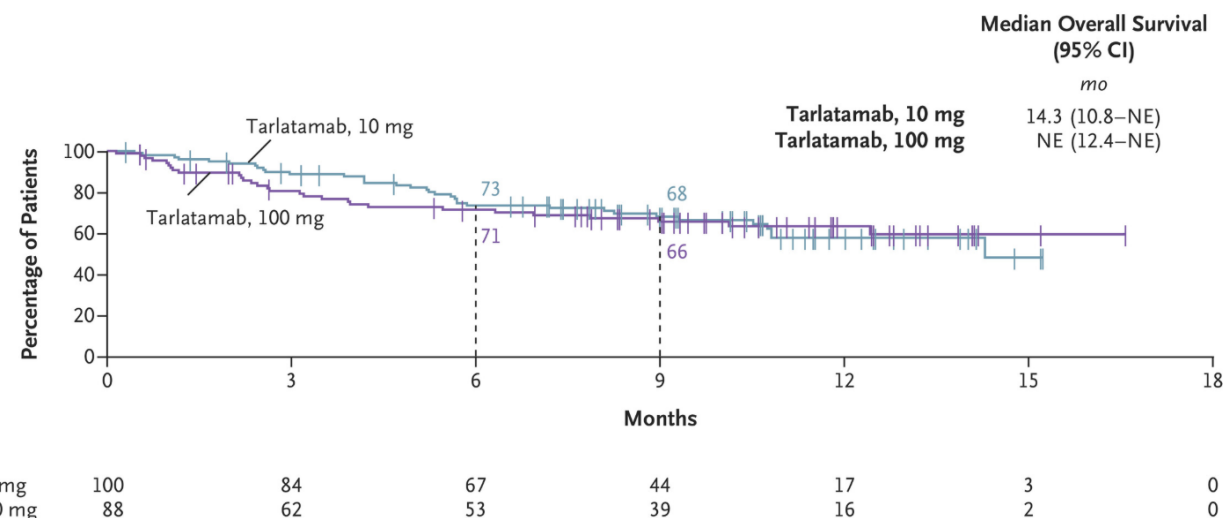
WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGIC TOXICITY including IMMUNE EFFECTOR CELL-ASSOCIATED NEUROTOXICITY SYNDROME

See full prescribing information for complete boxed warning.

Cytokine release syndrome (CRS), including life-threatening or fatal reactions, can occur in patients receiving IMDELLTRA. Initiate treatment with the IMDELLTRA using step-up dosing schedule to reduce the incidence and severity of CRS. Withhold IMDELLTRA until CRS resolves or permanently discontinue based on severity. (2.5, 5.1)

Neurologic toxicity and Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), including life-threatening or fatal reactions, can occur in patients receiving IMDELLTRA. Monitor patients for signs or symptoms of neurologic toxicity, including ICANS, during treatment and treat promptly. Withhold IMDELLTRA until ICANS resolves or permanently discontinue based on severity. (2.5, 5.2)

Overall Survival



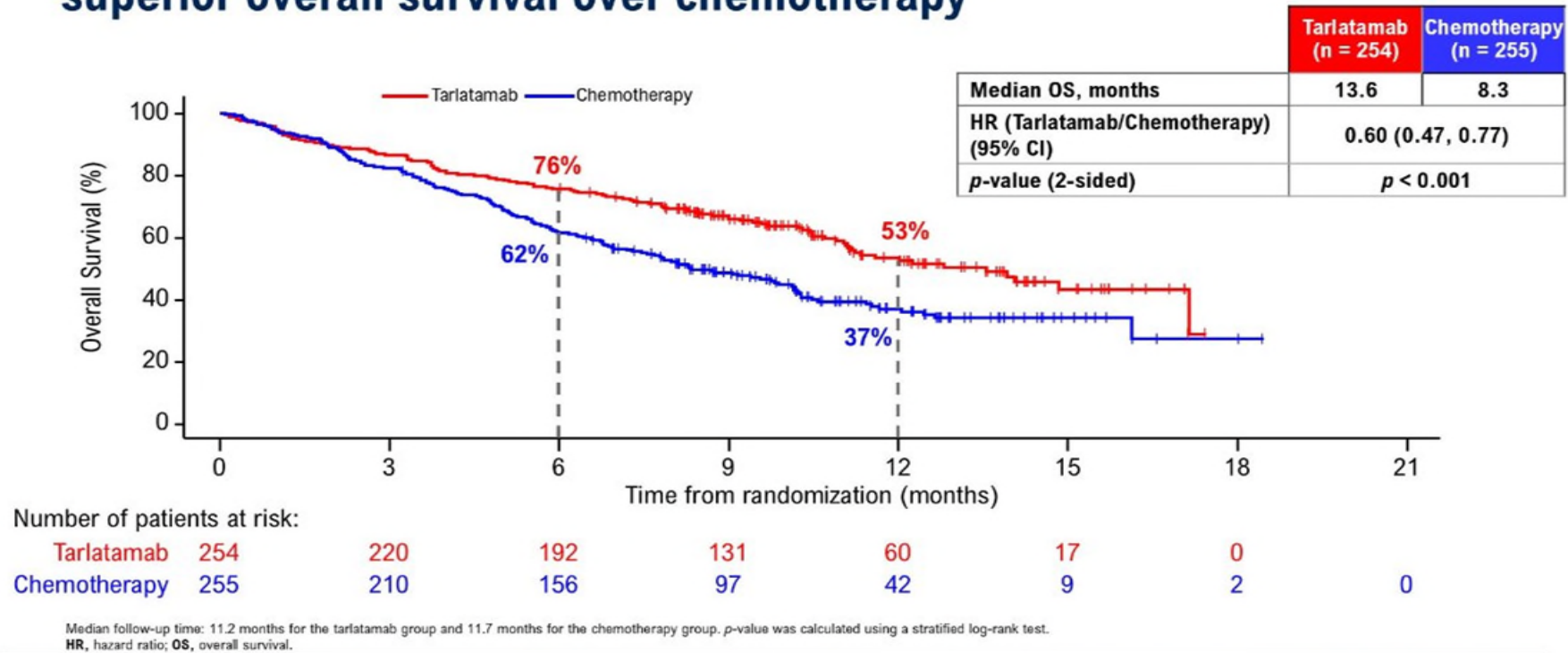
C1D1 and C1D8 require 22–24 hr observation

When is the improvement to OS worth the toxicity risk?



DeLLphi-304 (2025): 2L tarlatamab improved OS compared to SoC chemotherapy (13.6 vs. 8.3 mos)

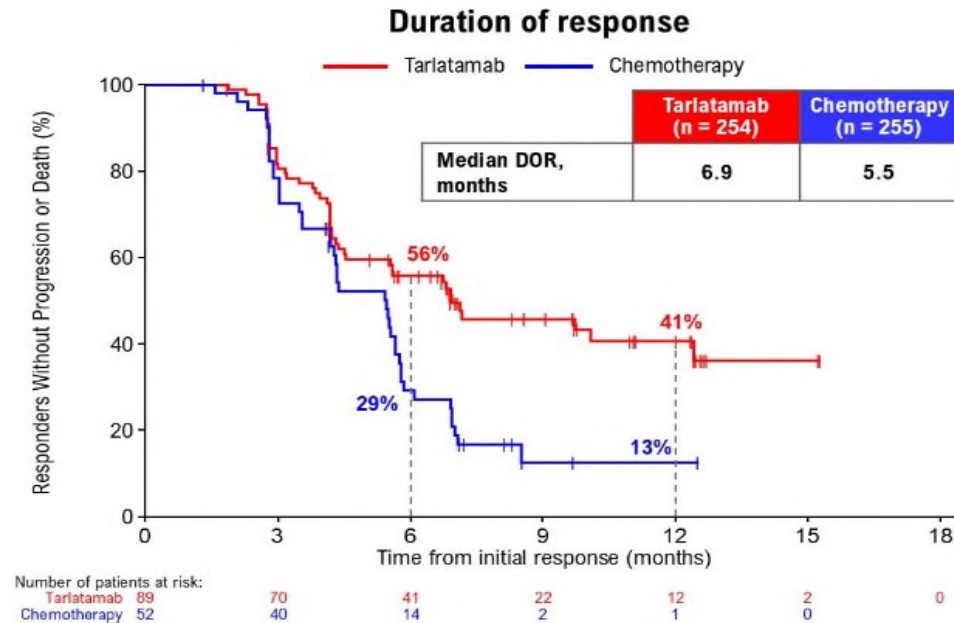
DeLLphi-304 met its primary endpoint with tarlatamab demonstrating superior overall survival over chemotherapy



DeLLphi-304 (2025): 2L tarlatamab improved ORR compared to SoC chemotherapy (35% vs. 20%)

Tarlatamab was associated with more frequent and more durable responses

	Tarlatamab (n = 254)	Chemotherapy (n = 255)
Best overall response^{*†}, n (%)		
Complete response	3 (1)	0 (0)
Partial response	86 (34)	52 (20)
Stable disease	84 (33)	112 (44)
Progressive disease	56 (22)	50 (20)
Not evaluable/no post-baseline scan	25 (10)	41 (16)
Objective response rate[‡], % (95% CI)	35 (29–41)	20 (16–26)
Median duration of response, months	6.9	5.5
Median time to objective response, months	1.5	1.4
Ongoing response at data cutoff, n[§] (%)	42 (47)	8 (15)



*Assessment of disease response was based on RECIST 1.1 guidelines. Confirmation of complete response and partial response was required no fewer than 4 weeks after initial documentation of complete response or partial response. [†]Investigator-assessed response in the intention-to-treat analysis set; [‡]Odds ratios and *p* value not shown as the difference in ORR between the 2 arms was not formally tested. [§]Percentage of total number of responders.

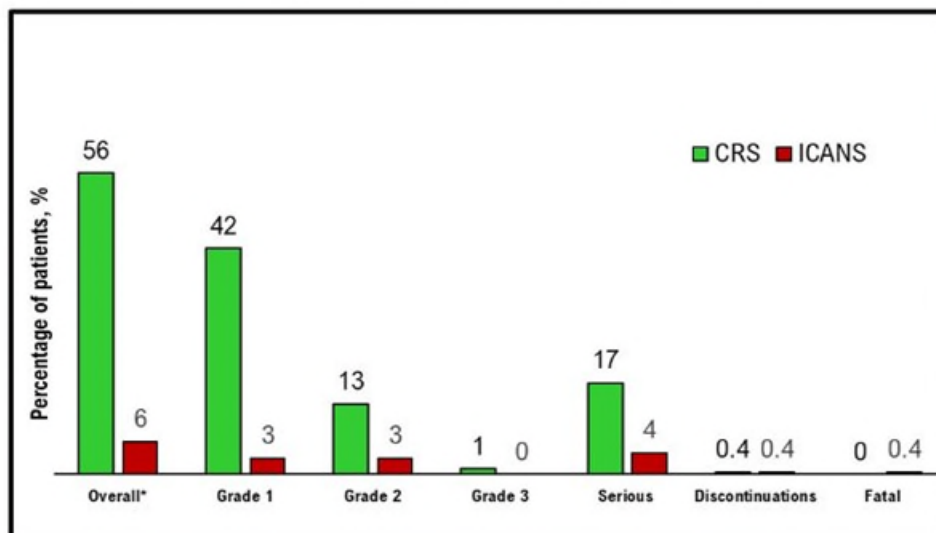
DOR, duration of response; IRECIST, Response Evaluation Criteria in Solid Tumors.



DeLLphi-304 (2025): Known CRS and ICANS risks remain

CRS and ICANS events were consistent with tarlatamab's established safety profile

Treatment-emergent CRS and ICANS with tarlatamab



CRS with first two infusions

Tarlatamab (N = 252)	Minimum required monitoring duration	
	6 - 8 Hours (n = 43)	48 Hours (n = 209)
Treatment emergent CRS, n (%)*	16 (37)	125 (60)
Grade 1	12 (28)	94 (45)
Grade 2	4 (9)	28 (13)
Grade 3	0 (0)	3 (1)
Serious adverse events	3 (7)	39 (19)
Leading to discontinuation of IP	0 (0)	1 (0.5)
Median time to intervention from last tarlatamab dose (hours)	17	27

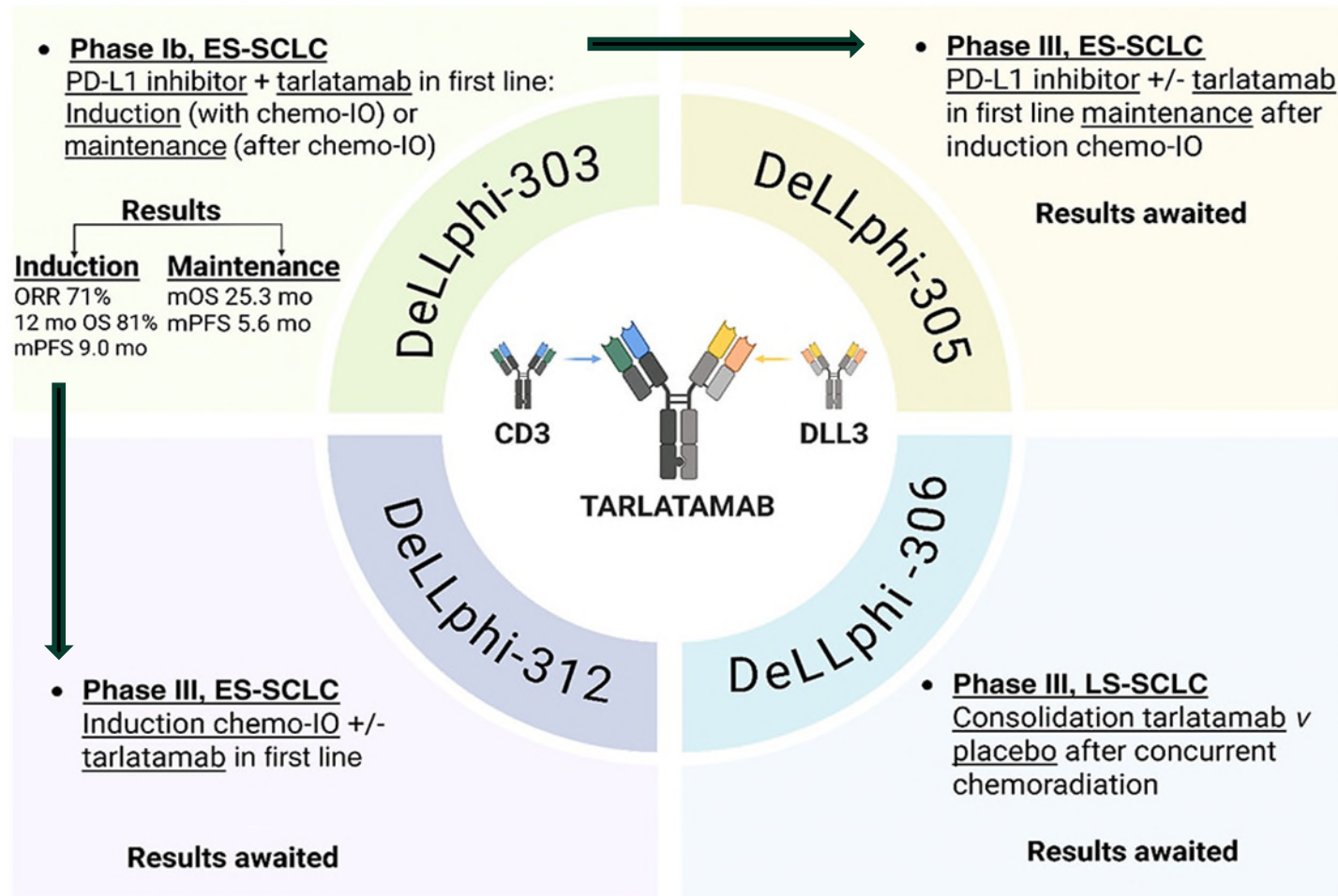
*Grade 4 CRS or ICANS events were not observed. A single grade 5 treatment-related adverse event observed with tarlatamab was attributed to ICANS in the setting of progressive neurological decline concurrent with persistent fever, hypoxemia, and hypotension.

CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; IP, investigational product.



Ongoing trials continue to evaluate tarlatamab across the treatment continuum

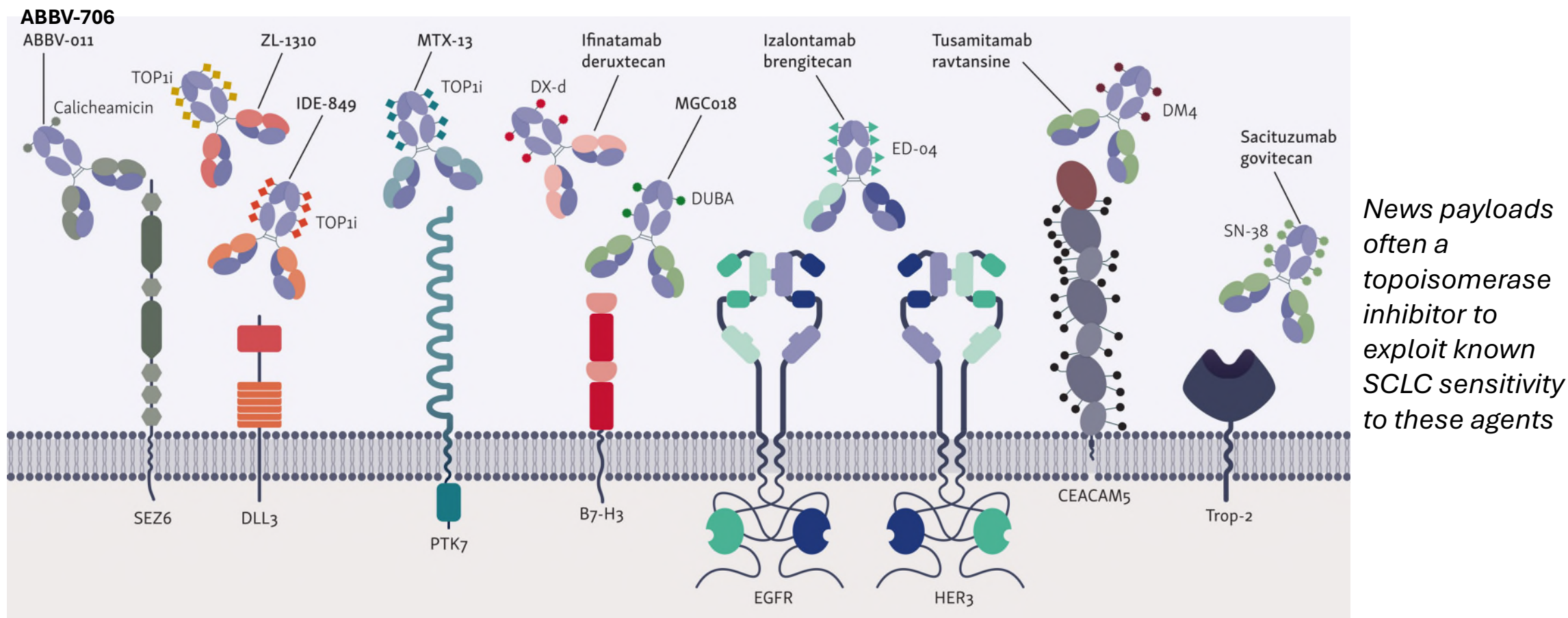
*Landmark
DeLLphi-303
results with
maintenance
mOS of 25.3
months!*



Additional bi- and trispecifics under investigation expand on the success of tarlatamab and address its limitations

Drug	Class	Mechanism of Action	Clinical Trial
Obrixtamig (BI 764532)	Bispecific	DLL3-CD3 BiTE	Phase I (NCT04429087)
			Phase I DAREON-8 (NCT06077500) (obrixtamig + 1L chemoimmunotherapy in ES-SCLC)
Peluntamig (PT 217)	Bispecific	DLL3-CD47 BiTE	Phase I/II (NCT05652686) (SKYBRIDGE study)
QLS31904	Bispecific	DLL3-CD3 BiTE	Phase I (NCT05461287)
Pumitamig	Antiangiogenic bispecific	PD-L1-VEGF	Phase II (NCT06449209)
Ivonescimab	Antiangiogenic bispecific	PD-1-VEGF	Phase I (NCT05116007)
Alvetamig (ZG 006)	Trispecific	DLL3-CD3 (two specific domains) TriTE	Phase I/II (NCT06283719)
Clesitamig (RO7616789)	Trispecific	DLL3-CD3-CD137 TriTE	Phase I (NCT05619744)
Gocatamig (MK-6070)	Trispecific (considered functionally a bispecific)	DLL3-CD3 BiTE	Phase I/II (NCT04471727)

Antibody Drug Conjugates (ADCs) also target SCLC biology



Promising ADC targets in SCLC based on disease profiling

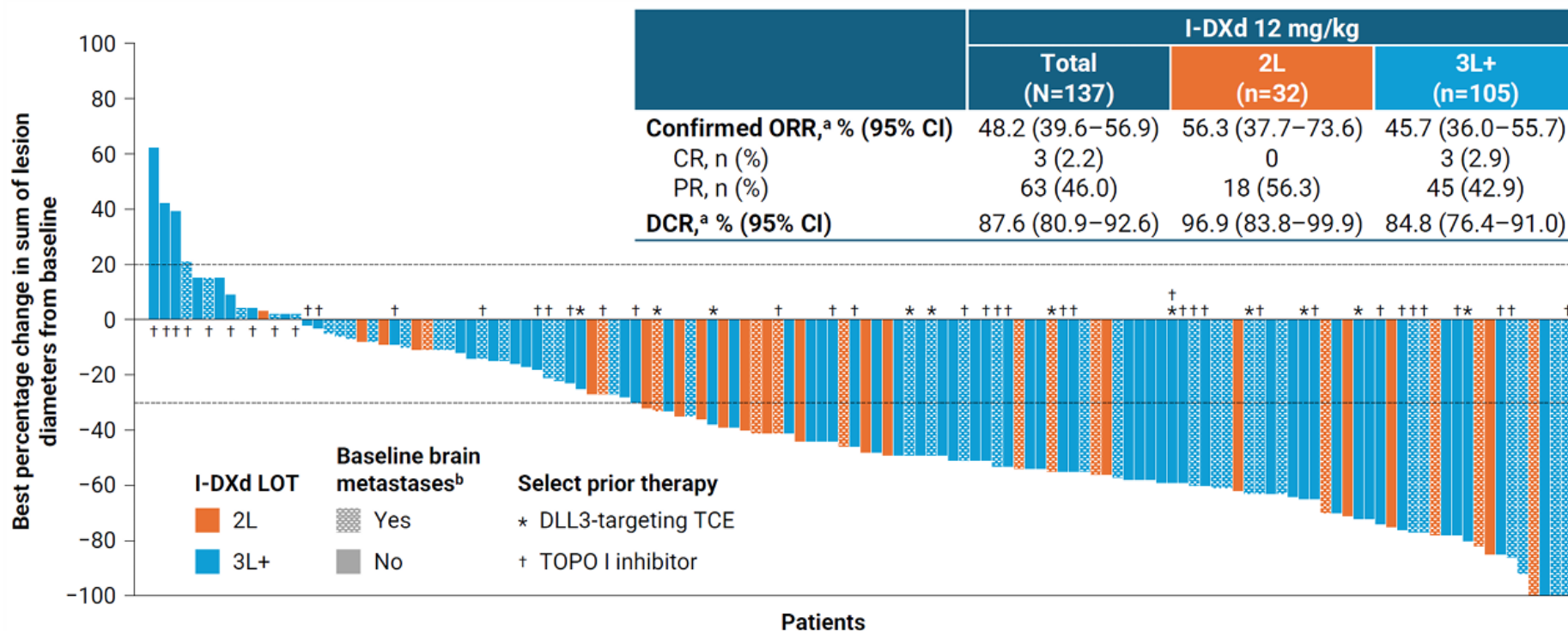
- **CD276**: Cluster of differentiation 276 (encodes **B7-H3**)
 - *I-DXd received a FDA Breakthrough Therapy Designation in August 2025*
- **DLL3**: Delta-like ligand 3
- **TACSTD2**: Tumor-associated calcium signal transducer (encodes trophoblast cell-surface antigen 2, **TROP2**)
 - *Sacituzumab govitevan received Breakthrough Therapy Designation in December 2024*
- **SEZ6**: Seizure related 6 homolog



IDeate-Lung01: Targeting B7-H3 (CD276) with ifinatamab deruxtecan (I-DXd) in ES-SCLC



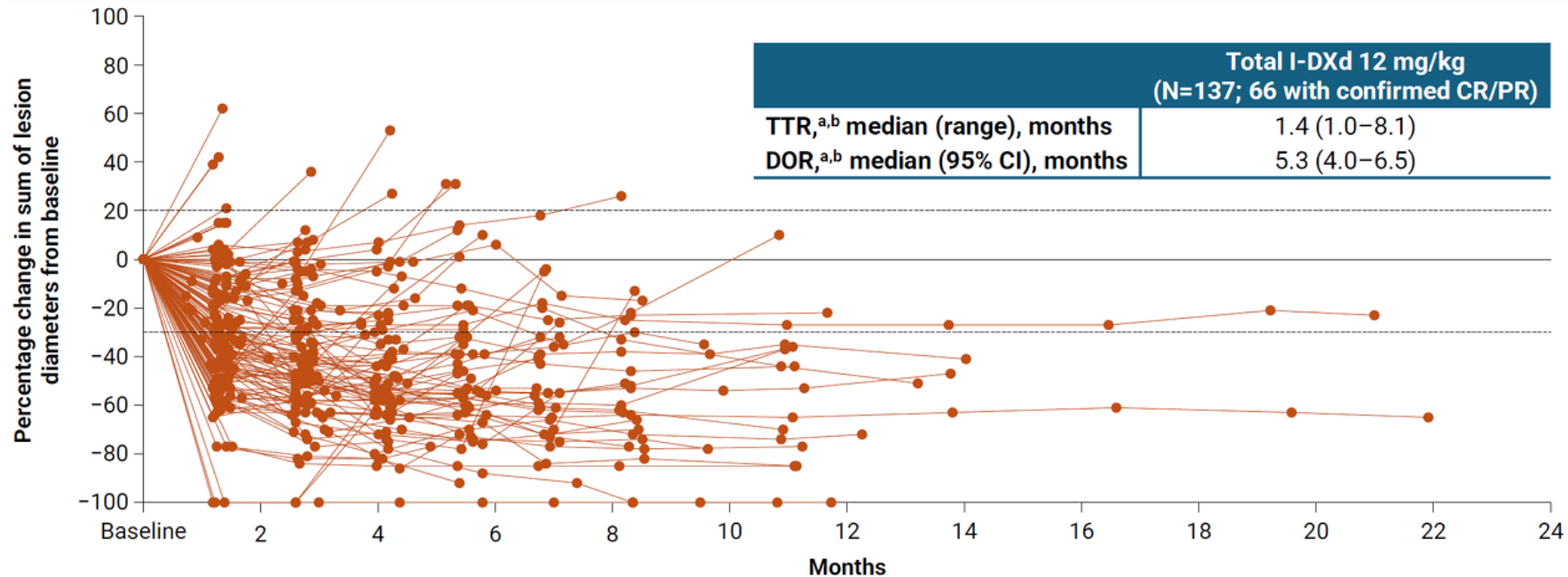
I-DXd 12 mg/kg demonstrated promising antitumor activity



IDEate-Lung01: Targeting B7-H3 (CD276) with ifinatamab deruxtecan (I-DXd) in ES-SCLC



Responses with I-DXd 12 mg/kg were rapid and durable



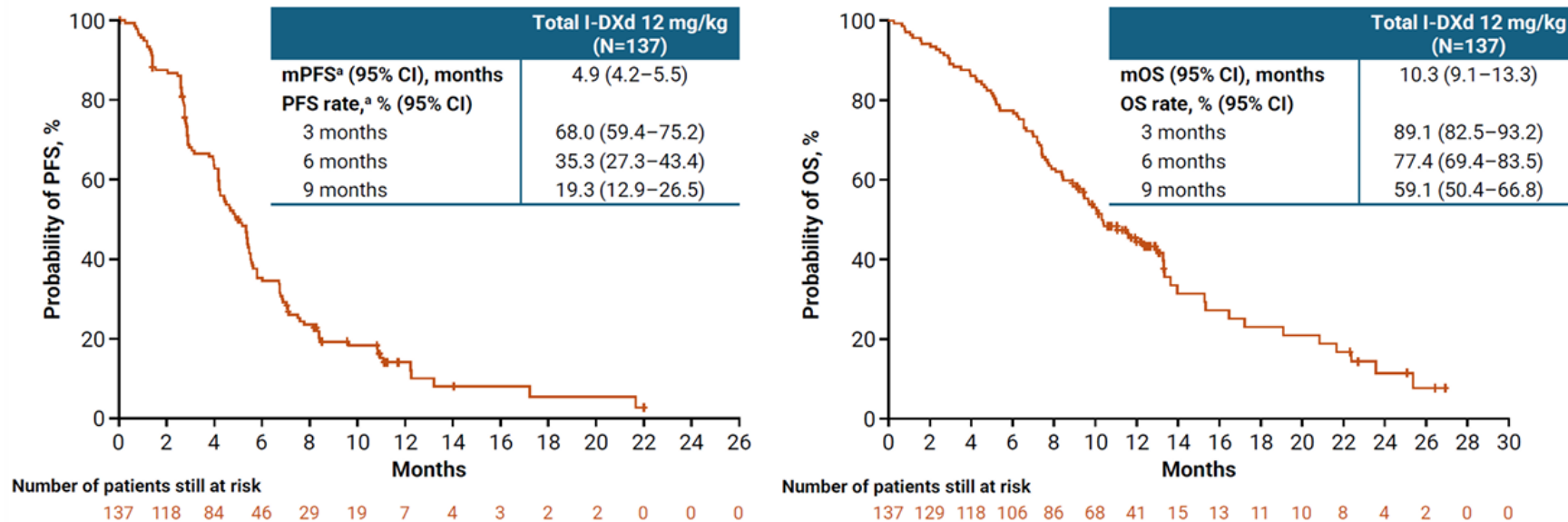
Among patients who received I-DXd 12 mg/kg as 2L therapy (n=32), median TTR was 1.4 months (range, 1.2–4.0) and median DOR was 7.2 months (95% CI, 3.6–NE)



IDEATE-Lung01: Targeting B7-H3 (CD276) with ifinatumab deruxtecan (I-DXd) in ES-SCLC



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

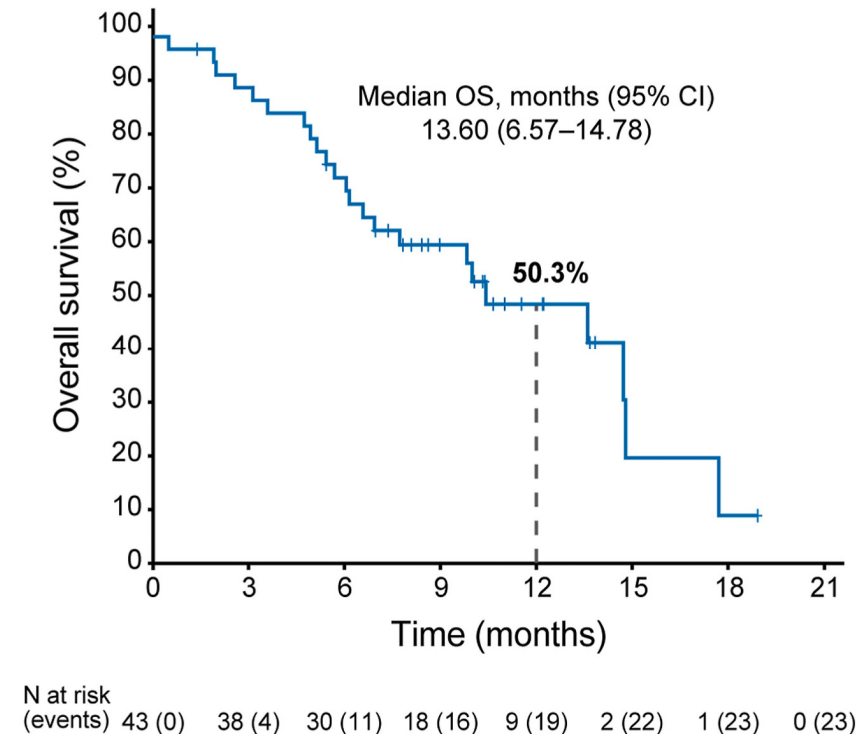
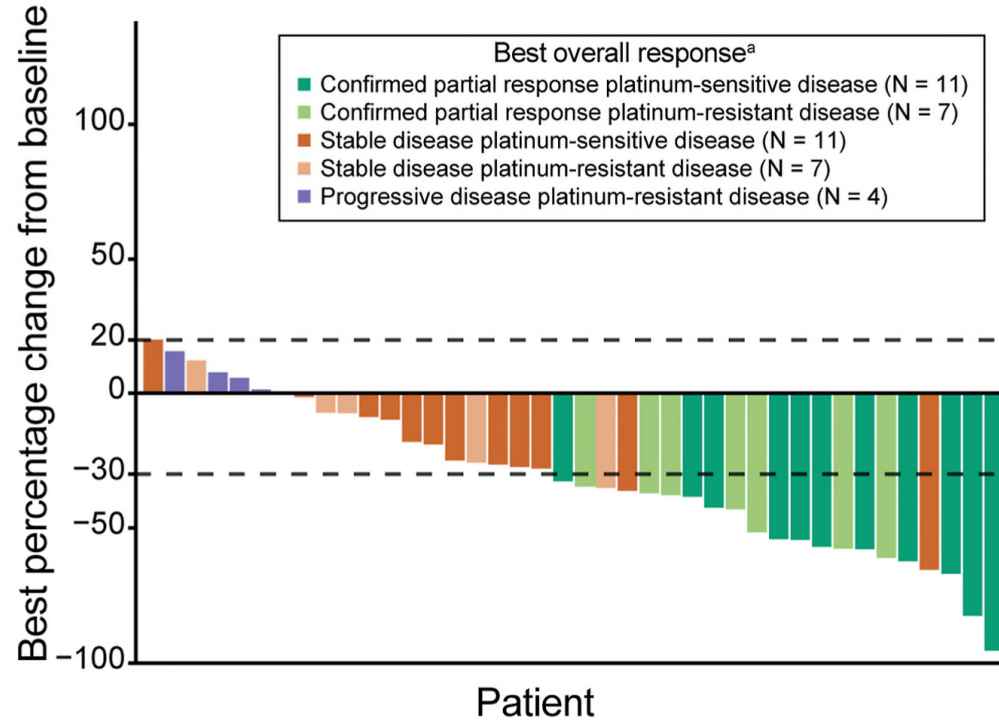


Among patients who received I-DXd 12 mg/kg as 2L therapy (n=32), mPFS was 5.6 months (95% CI, 3.9–8.1) and mOS was 12.0 months (95% CI, 7.3–19.1)

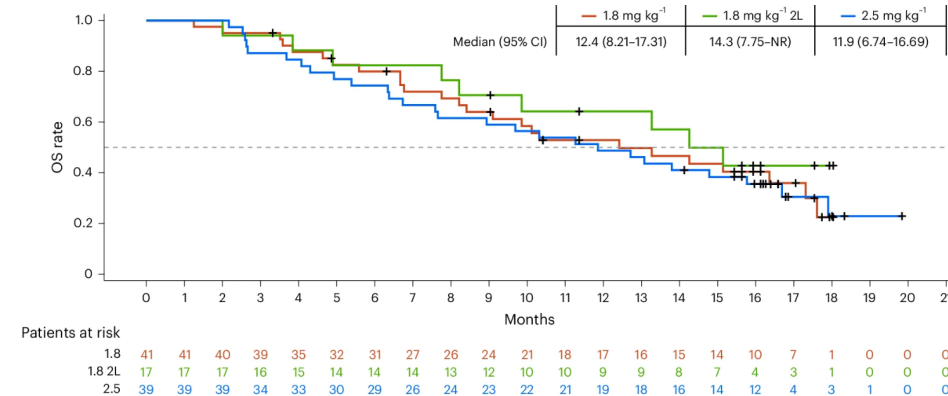
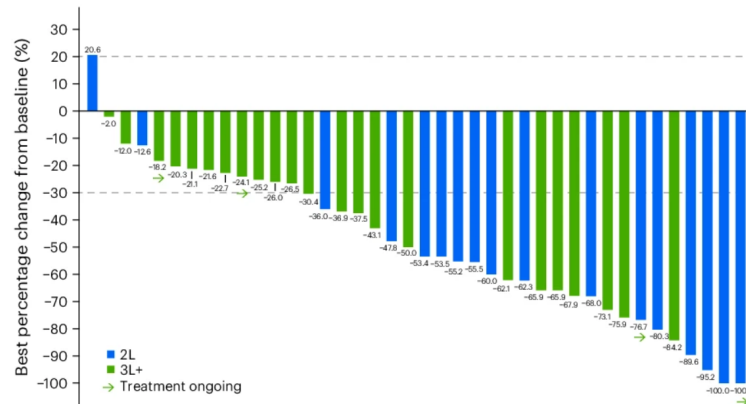


TROPiCS-03: High response rates to targeting TROP2 with sactizumab govetican in ES-SCLC

- 2L setting in patients progressing after platinum-based chemo and anti-PD-(L)1 therapy
- OOR was 41.9% and OS was 13.60 months

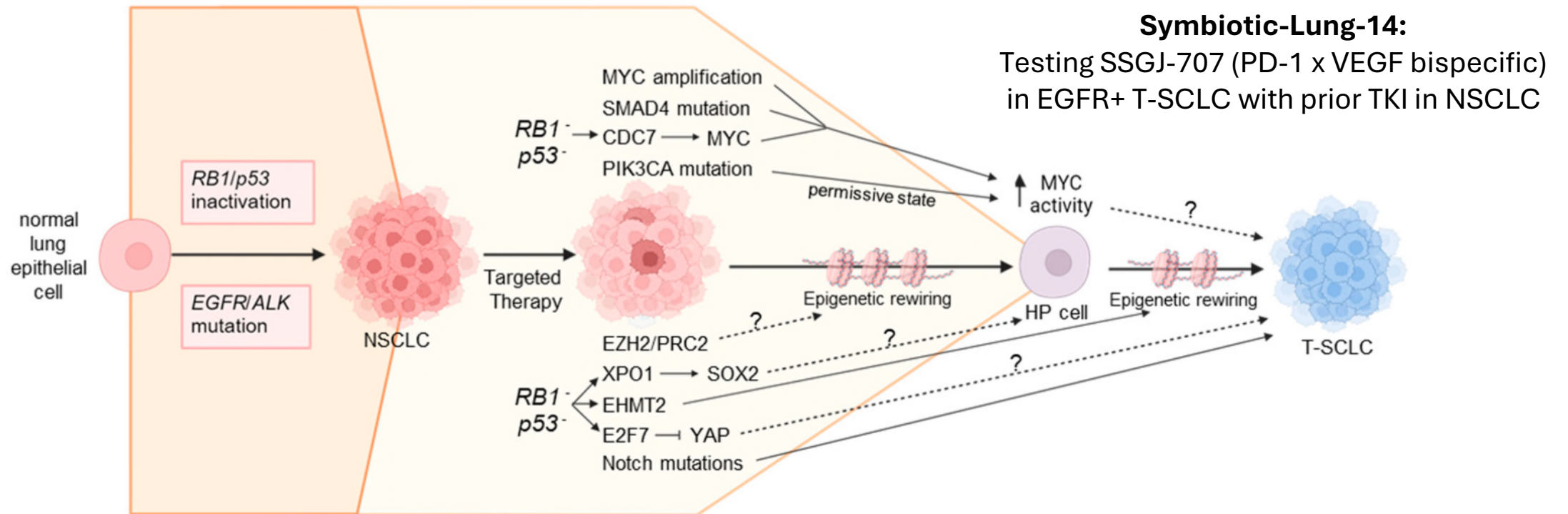


ABBV-706: High OOR and promising efficacy outcomes with SEZ6-targeting ADC in 1L and 2L setting



	Part 2a: 1.8 mg kg ⁻¹ (n = 41)	Part 2a: 1.8 mg kg ⁻¹ , 2L (n = 17)	Part 2a: 2.5 mg kg ⁻¹ (n = 39)
ORR, n (%)	23 (56.1)	14 (82.4)	23 (59.0)
(95% CI)	(39.7-71.5)	(56.6-96.2)	(42.1-74.4)
Clinical benefit rate, n (%)	39 (95.1)	16 (94.1)	37 (94.9)
(95% CI)	(83.5-99.4)	(71.3-99.9)	(82.7-99.4)
Median DOR, months (95% CI)	5.93 (3.55-11.10)	6.57 (3.12-12.45)	4.88 (3.52-6.87)
Median PFS, months (95% CI)	6.44 (4.01-8.08)	6.77 (4.01-12.45)	5.62 (4.44-7.03)
Median OS, months (95% CI)	12.42 (8.21-17.31)	14.26 (7.75-NE)	11.86 (6.74-16.69)

Transformation of NSCLC to SCLC: A mechanism of resistance to targeted therapies



We may need a new focus on T-SCLC as more targeted therapies are developed for NSCLC.

The Future of Treating SCLC

Unanswered Questions

- Which patients should get what therapy?
- When should treatments be incorporated and in what sequence?
- When should biomarkers be sampled for identification?
- How does biomarker information change our strategy?

Next Generation Therapies

- Continued development of targeted therapies based on lineage-specific biomarkers (DLL3, SEZ6)
- Novel ways to engaged the immune system and CAR T cell therapies
- Cross fertilization across neuroendocrine tumors to expand impact
- PROTACs? Gene therapies?

A renewed enthusiasm for studying this recalcitrant malignancy!



Thank you for your kind attention!

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