Fred Hutch Cancer Center

Small Cell Lung Cancer

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Comprehensive Hem/Onc Review Course
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UW Medicine

I have no relevant disclosures.

Additional Slide Credit to Dr. Nick Giustini

A quick post lunch poem…

This Is Just To Say
Wililam Carlos Williams

I have eaten
the plums
that were in
the icebox

and which
you were probably
saving
for breakfast

Forgive me
they were delicious
so sweet
and so cold

Goals and Objectives

- Review the clinical presentation and work-up of SCLC
- Review the pathologic characteristics of SCLC
- Review SCLC staging
- Discuss treatment of limited stage SCLC
- Discuss treatment of extensive stage SCLC

Background & Diagnosis

Background

- 10-15% of lung tumors
- Occurs almost exclusively in smokers
- Rapid doubling time and early distant spread
- Tends to present as metastatic disease (>70%)
- Remains a very deadly disease (12-15% five-year OS for all stages)

Kim, So Yoen., et al. *JAMA*. 2025;333;(21):1906-1917.

Clinical Presentation

- Central lung mass with bulky mediastinal adenopathy
  - Metastases: liver, adrenals, **brain (15%)**, bone, bone marrow
- Patients often highly symptomatic
  - Pulmonary symptoms
  - **Systemic symptoms** (pretreatment ECOG)
  - Compression symptoms: **Superior Vena Cava (SVC)** syndrome (10%, treat with chemo)
  - Paraneoplastic syndromes

Kim, So Yoen., et al. *JAMA*. 2025;333;(21):1906-1917.

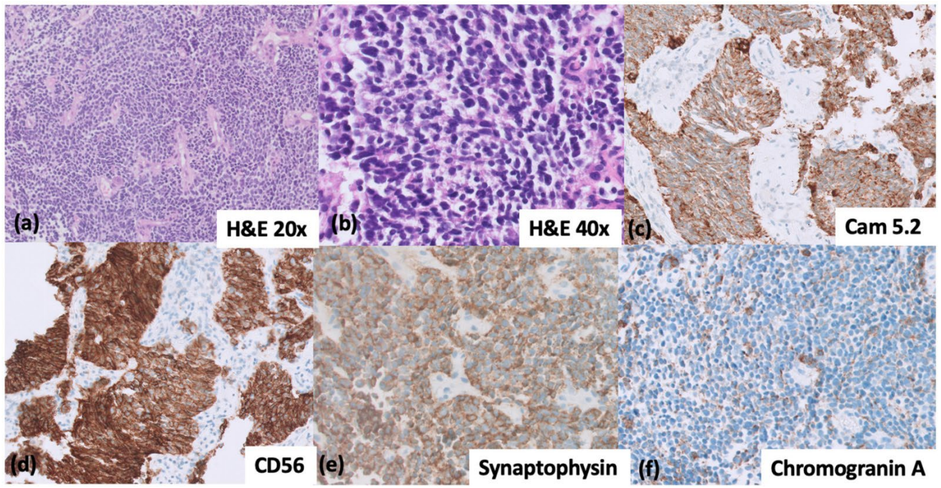
Clinical Presentation: Paraneoplastic Syndromes

Syndrome	Etiology	Signs and Symptoms	% SCLC with syndrome	% syndrome with SCLC
SIADH	Ectopic ADH secretion (>> low Na)	Hyponatremia, low serum Osm with high urine Osm, weakness, confusion Refractory Tx: Tolvaptan	15-40%	--
Cushing syndrome	Ectopic ACTH secretion (>> excess cortisol)	Hyperglycemia, hypokalemia, edema, hypertension, muscle weakness	2-5%	3-11%
Lambert-Eaton myasthenic syndrome (LEMS)	Antibodies to **voltage gated Ca channels**	Proximal muscle weakness and fatigability that improves with repetitive stimulation ie EMG (vs myasthenia gravis)	3%	50%
Limbic encephalitis	Antibodies to **Hu family proteins**	Personality and psychiatry changes, seizures, memory loss	<1%	50%
Paraneoplastic cerebellar degeneration	Numerous antibodies (Hu, YO, CRMP-5, Pca-2, MA1, etc.)	Acute dizziness and nausea/vomiting> gait instability, truncal ataxia, dysarthria, ocular findings, vertigo	<1%	5%

Van Meerbeeck., et al. *Lancet*. 2011;378:1741-1755.

Diagnosis: Recommended Work-up

- Labs (CBC, BMP, LFTs, uric acid?)
- Pathology review:
  - IHC with Neuroendocrine differentiation, TTF1 (>85%)
  - High grade (>10 mitoses/2mm2, Ki-67 of 50-100%)
- CT chest/abdomen/pelvis with contrast
- MRI brain



- PET if limited stage disease suspected (alternative: bone scan + CT CAP)
- Mediastinal staging if tumor < 5 cm, clinically node-negative (cT1-2 N0)

NCCN Guidelines: Small Cell Lung Cancer. Version 2.2026.; Keogh et al. Cancers 2022, 14(15), 3772

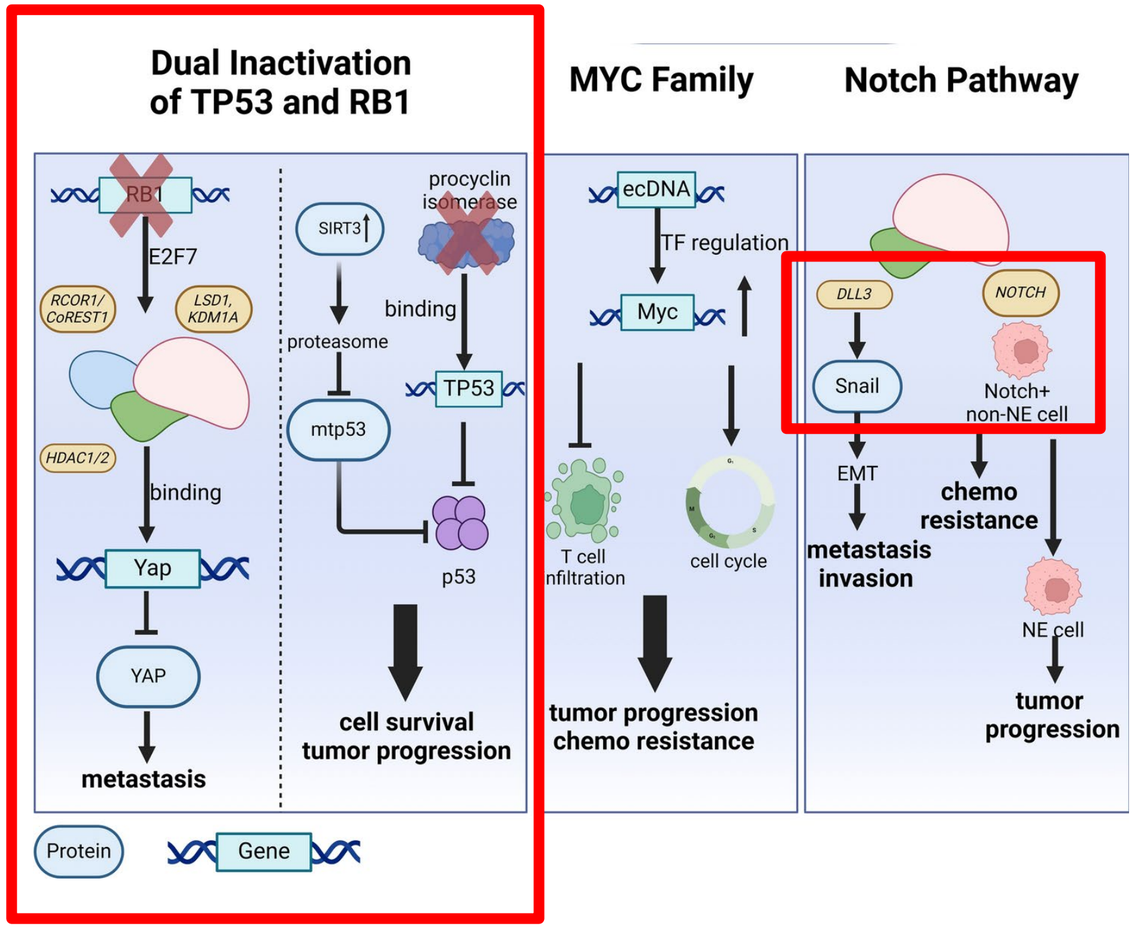
Molecular signature

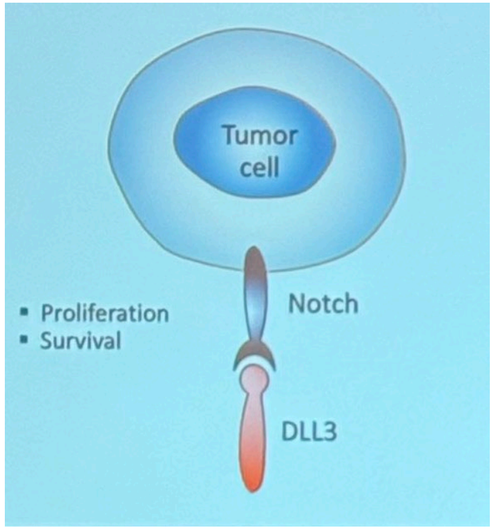
Genomic:

Ubiquitous (100%) **TP53 and RB1 loss**

Common MYC mutations

Unlike NSCLC, no targetable oncogenes





DLL3 expressed on surface of >80-85% SCLC cells (and NOT normal tissue)

Zhai et al. Journal of Hematology and Oncology, 2025

Staging

Stage	Description
Limited (I-III; 30-40%)	Tumor must be encompassed by tolerable XRT field (i.e. in one hemithorax + regional nodes, no pleural effusion)
Extensive (IV; 60-70%)	All disease that is not limited stage

Management: Limited Stage

Management: Limited Stage SCLC

- T1-T2 (tumor <5 cm), **N0 *(confirmed by mediastinal staging)***
  - Resection (pN0) → adjuvant cisplatin/etoposide x4 cycles
  - Resection (pN1 or pN2) → adjuvant cisplatin/etoposide x4 cycles + XRT
- All other limited stage
  - Concurrent cisplatin/etoposide x4 cycles + concurrent XRT → adjuvant durvalumab

NCCN Guidelines: Small Cell Lung Cancer. Version 2.2026

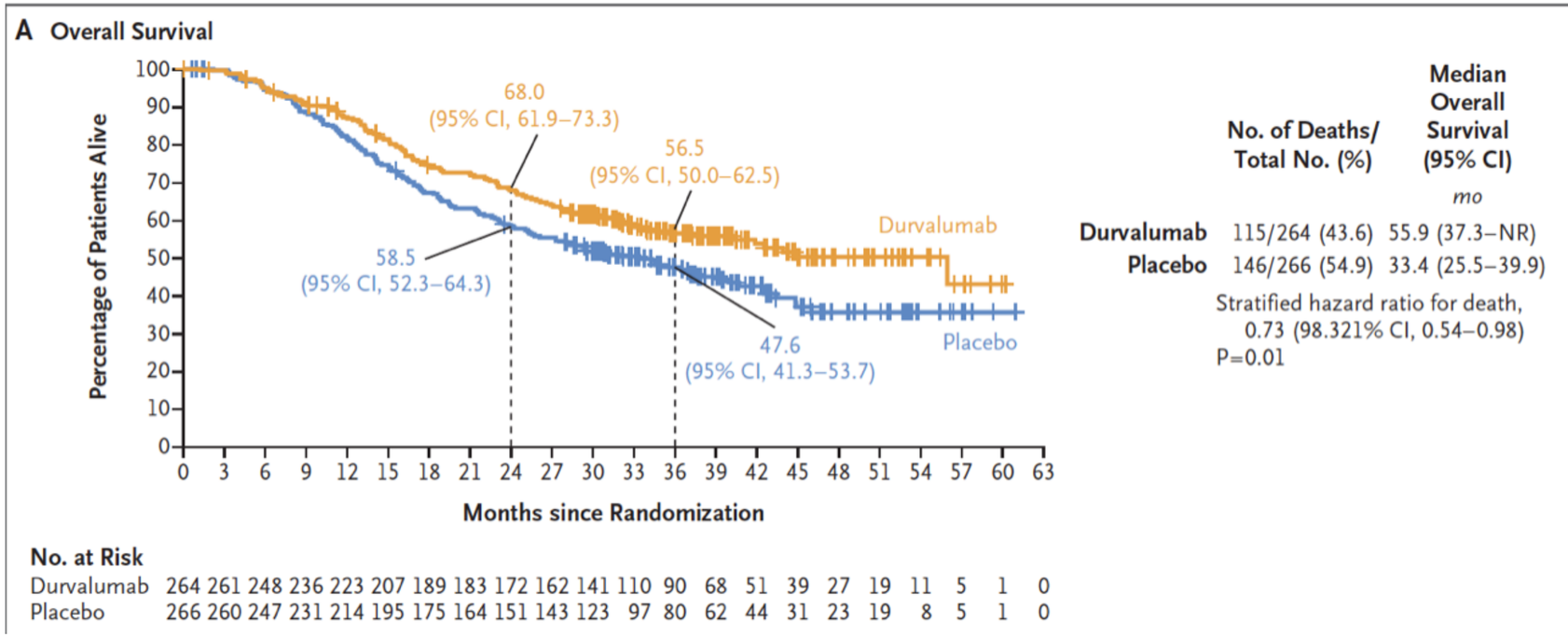
FDA approval 12/2024

Management: Limited Stage SCLC

- ADRIATIC: durvalumab vs placebo x2 years if **no PD after concurrent Platinum CRT** +/- PCI

Take home point **~30% reduction in risk of death with use of adjuvant immunotherapy**

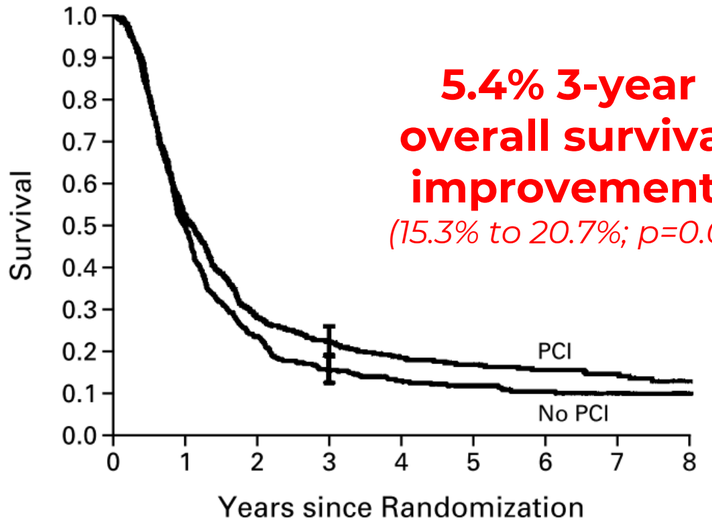
PFS 16.6 vs 9.2 mo (HR 0.76; 0.58-0.98)



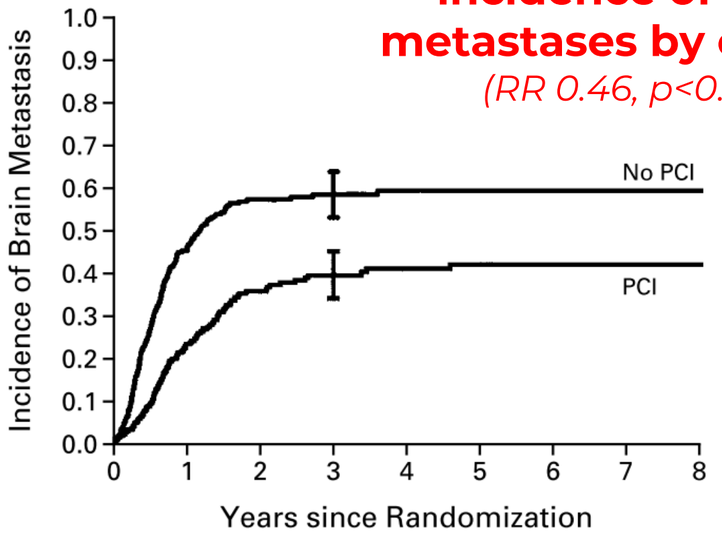
Cheng, Y. et al, NEJM, 2024; 391: 1313-27.

Management: Limited Stage SCLC

Prophylactic Cranial Irradiation (PCI)



5.4% 3-year overall survival improvement:
(15.3% to 20.7%; p=0.01)



Decrease cumulative incidence of brain metastases by one half
(RR 0.46, p<0.001)

No. at Risk									
No PCI	461	224	103	61	44	34	23	19	15
PCI	526	276	139	101	66	52	40	29	17

No. at Risk									
No PCI	457	171	88	57	41	32	21	18	14
PCI	524	248	133	96	66	52	40	29	17

Auperin A, et al. *NEJM*. 1999;341:476-84.

Prophylactic Cranial Irradiation Caveats

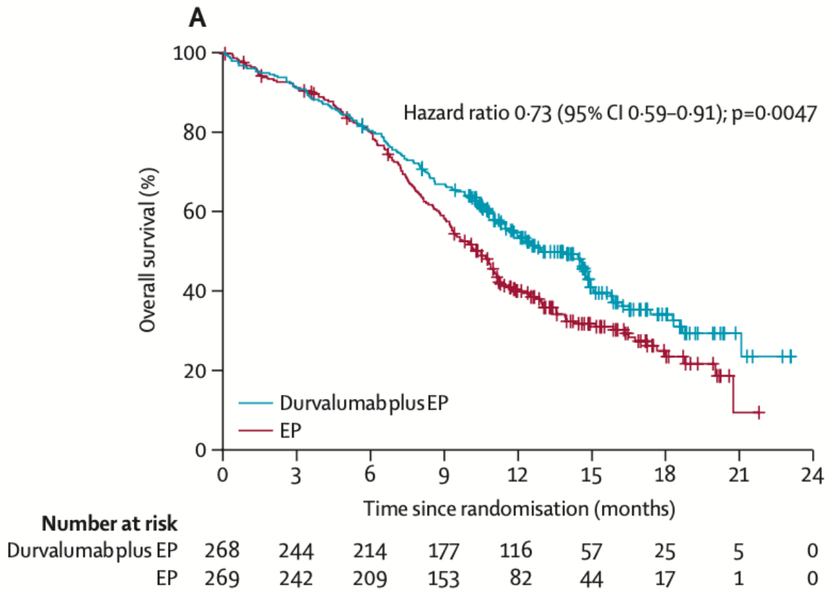
- Most strongly recommended in patients with LS-SCLC with **good upfront response to chemoradiation** (partial or complete response)
  - Benefit unclear if stable disease or for earlier stage tumor (T1-T2aN0)
  - Utilize neuro-protective measures: **hippocampal sparing and memantine**
- **Consideration MRI surveillance over PCI** in patients with poor performance status, neurocognitive impairments, or older age (>60)
  - Chronic neurotoxicity 83% (≥ 60 yo) vs 56% (< 60 yo)

Wolfson, A., et al. *Int J Radiat Oncol Biol Phys*. 2010;81(1):77-84.
NCCN Guidelines: Small Cell Lung Cancer. Version 2.2026.

Management: Extensive Stage

Management: Extensive Stage SCLC

Carboplatin + etoposide + IO (atezo vs durva) x4 cycles → IO maintenance

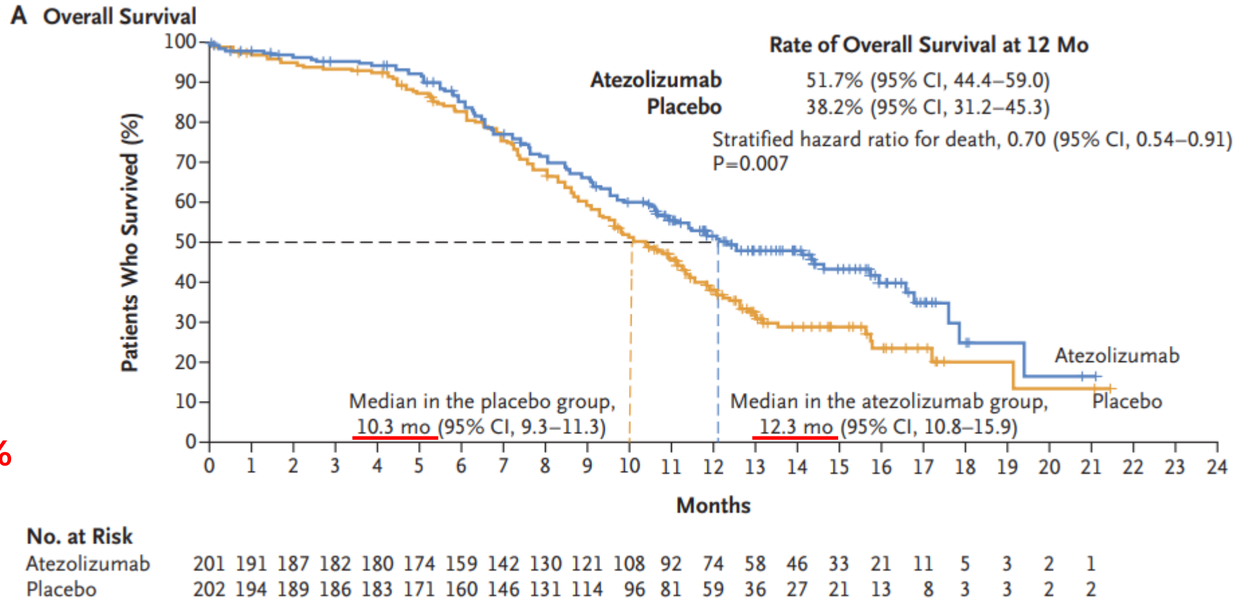


~30% reduction in risk of death with IO

mOS 12-13 mo,

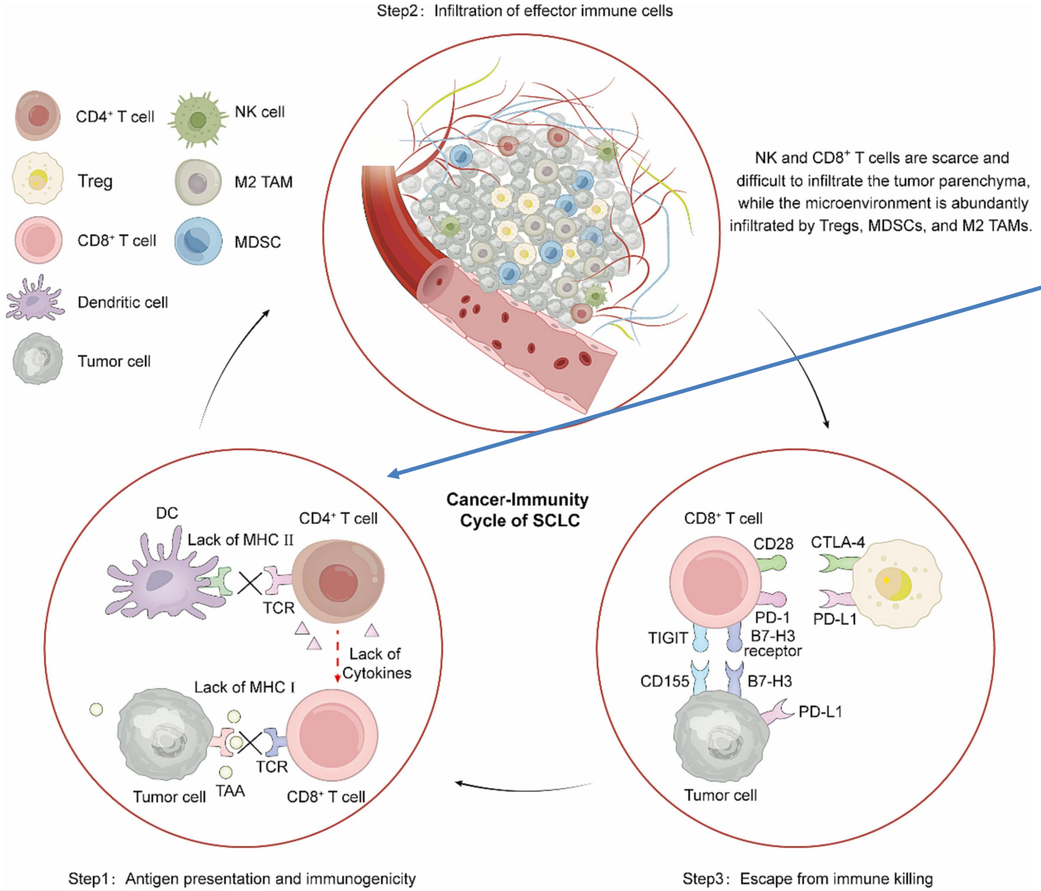
mPFS ~5 mo

5-year OS 10-12%



Horn L, et al. *NEJM*. 2018;379(23):2220-29.
Paz-Ares L, et al. *Lancet*. 2019;394(10212):1929-39.

Poor IO response due to immune evasion of SCLC



1. **Downregulation MHC I and II**
   (dysfunction of antigen presentation needed for adaptive immunity/T-cell killing)

2. **Immunosuppressive environment**
   (IL-2 down and IL-15 up)

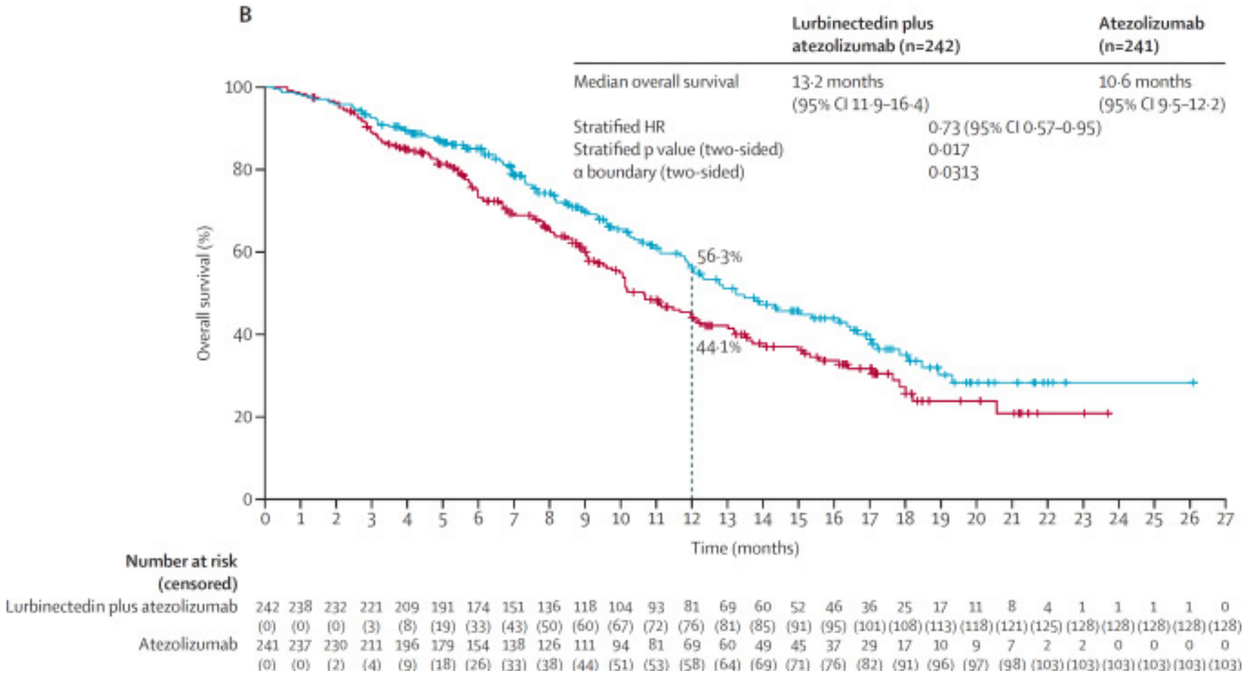
3. **Downregulated PDL1**
   (abundant in NSCLC, present in <1% tumor samples on clinical trial)

Tian et al, Journal of Heme & Onc 2019
Chen et al, CA Tx Reviews 2023

FDA Priority Approval (10/2/25)

Management: Maintenance Lurbi?

Carboplatin + etoposide + Atezo x4 cycles→ **(ECOG 0-1)** → Atezo + Lurbinectedin maintenance vs Atezo (IMFORTE)



Gain <3 months overall survival (mOS 13.2 vs 10.6)

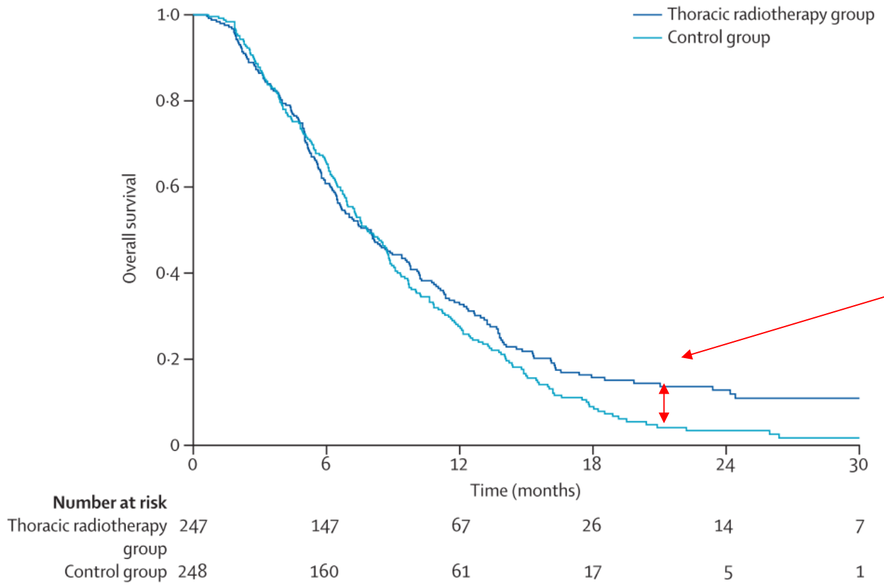
Treatment related G3/4 AEs 25.6% vs 5.8%

Take Home:
Great consideration for fit, young patients

Paz-Ares, L. et al, Lancet ,2025 (405), p2129-2143.

Management: Extensive Stage SCLC

- Can consider consolidative thoracic XRT in select patients after chemo
  - Trial enrolled pt with good chemo response, received PCI, ECOG 0-2

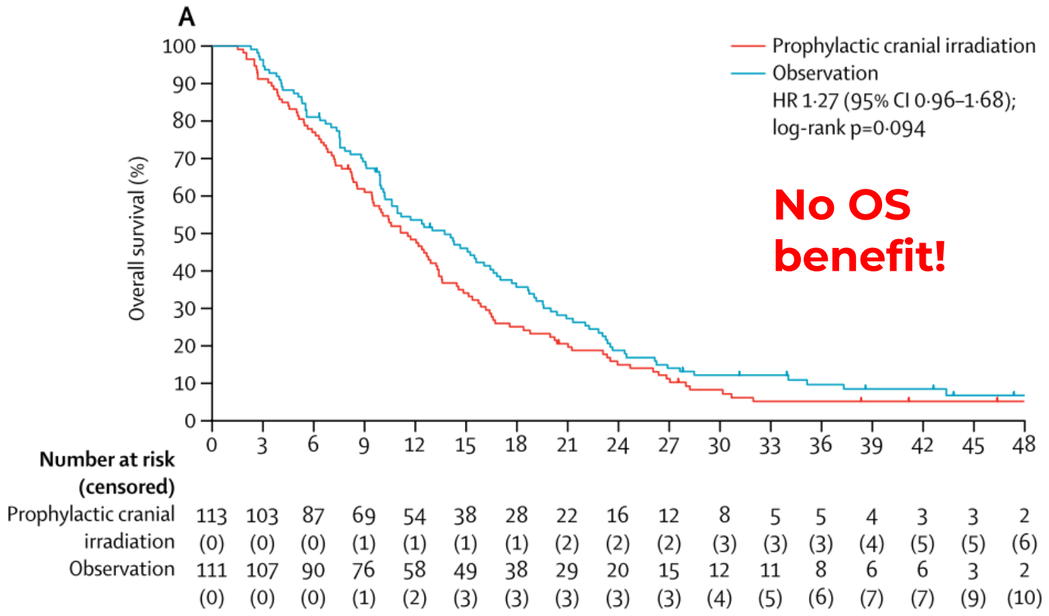


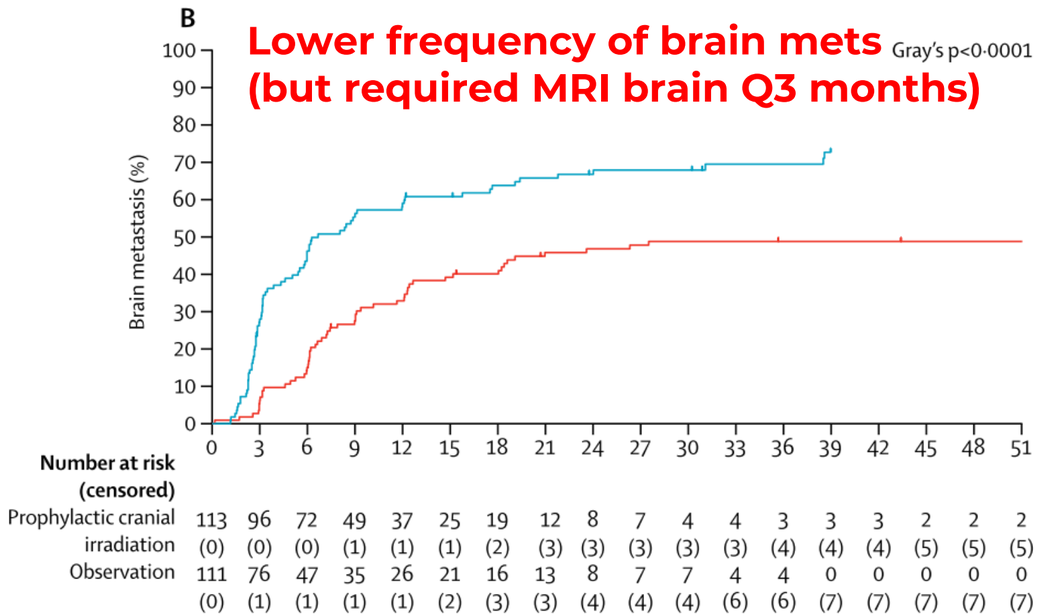
- Median PFS 4 vs 3 months (NS)
- 1 year OS primary endpoint NS
  - **OS benefit not until 2 years** (13% vs 3%; p=0.004)
- **Improved intrathoracic control**
  - Reduced Intrathoracic PD, 43.7% vs 79.8%, p<0.0001)

Slotman BJ, et al. *Lancet*. 2015;385:36-42.
Slotman BJ, et al. *Lancet*. 2015;385:1292-1293.

Management: Extensive Stage SCLC

- PCI no longer standard of care → MRI brain surveillance





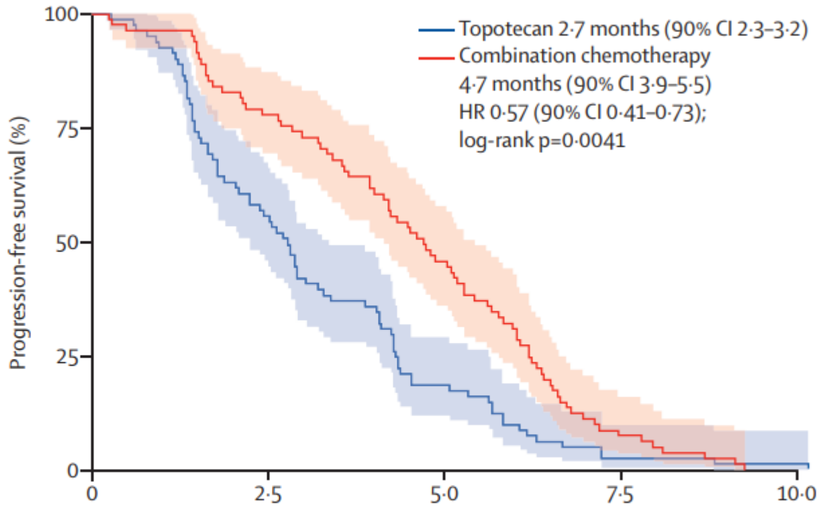
Takahashi T, et al. *Lancet Oncol*. 2017;18:663-71.

Management: Relapse

- Therapy depends on timing of relapse after last platinum doublet
  - ≤ 6 months use alternative agent
  - > 3-6 months retreat with platinum doublet

Management: Relapse

- > 3-6 months: carboplatin/etoposide rechallenge

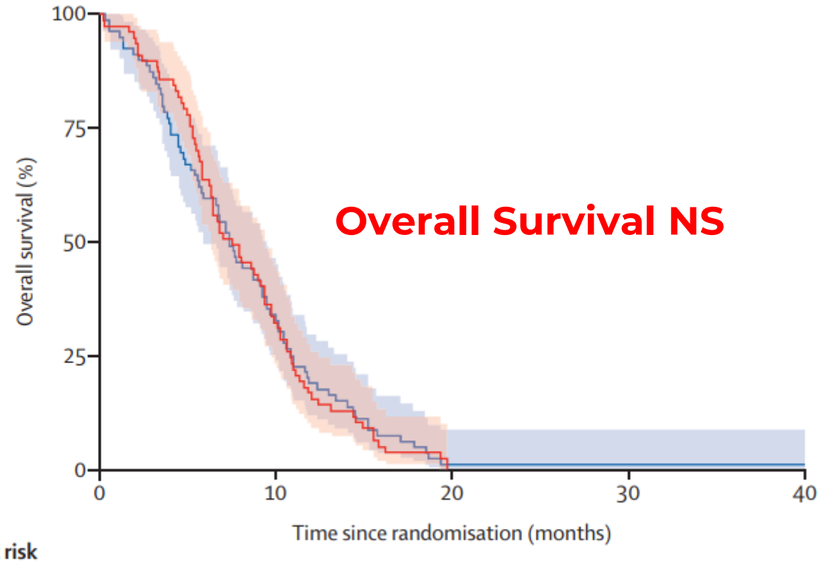


Number at risk (numbers censored)					
Topotecan	81 (0)	45 (0)	15 (0)	2 (0)	1 (0)
Combination chemotherapy	81 (0)	63 (0)	7 (0)	6 (2)	0 (2)

Reduced chance of progression by ~40%

PFS subgroup analysis (time to rechallenge)

- 90-180 days: HR 0.70 (CI 0.57-1.05)- **NS**
- **180+ days: HR 0.23 (CI 0.18-0.62)**



Overall Survival NS

Number at risk (numbers censored)					
Topotecan	79 (0)	27 (0)	15 (0)	2 (2)	1 (2)
Combination chemotherapy	77 (0)	25 (0)	0 (0)	0 (4)	0 (5)

Baize N, et al. *Lancet Oncol*. 2020;21(9):1224-33.

Management: Relapse

- ≤ 6 months: second line treatment
  - **Tarlatamab***
  - Lurbinectedin*
  - Topotecan*
  - Taxane
  - Irinotecan
  - Gemcitabine

*FDA approved for second line+

Management: Relapse

FDA accelerated approval 05/2024

- Tarlatamab = bispecific T cell engager (CD3 / DLL3), DeLLphi-304

Exceeds survival outcomes for all 1L treatment (mOS 13.6 mo) **with 40% improvement in OS from SOC chemo.**

Will there be a tail?

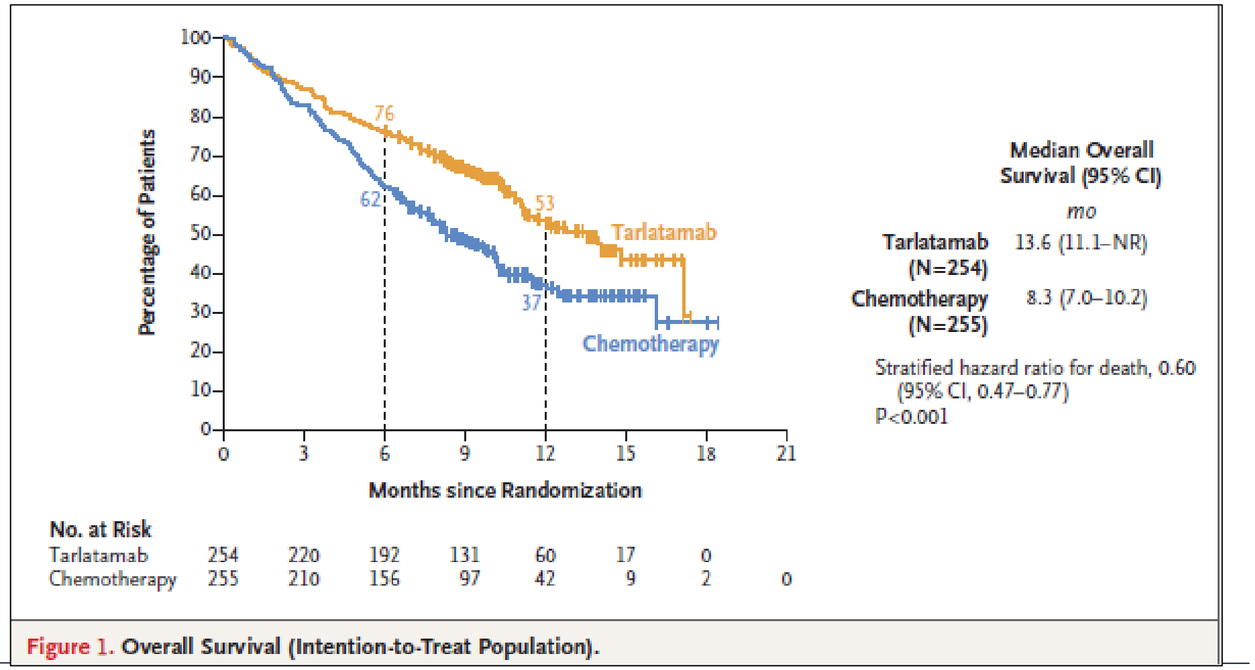
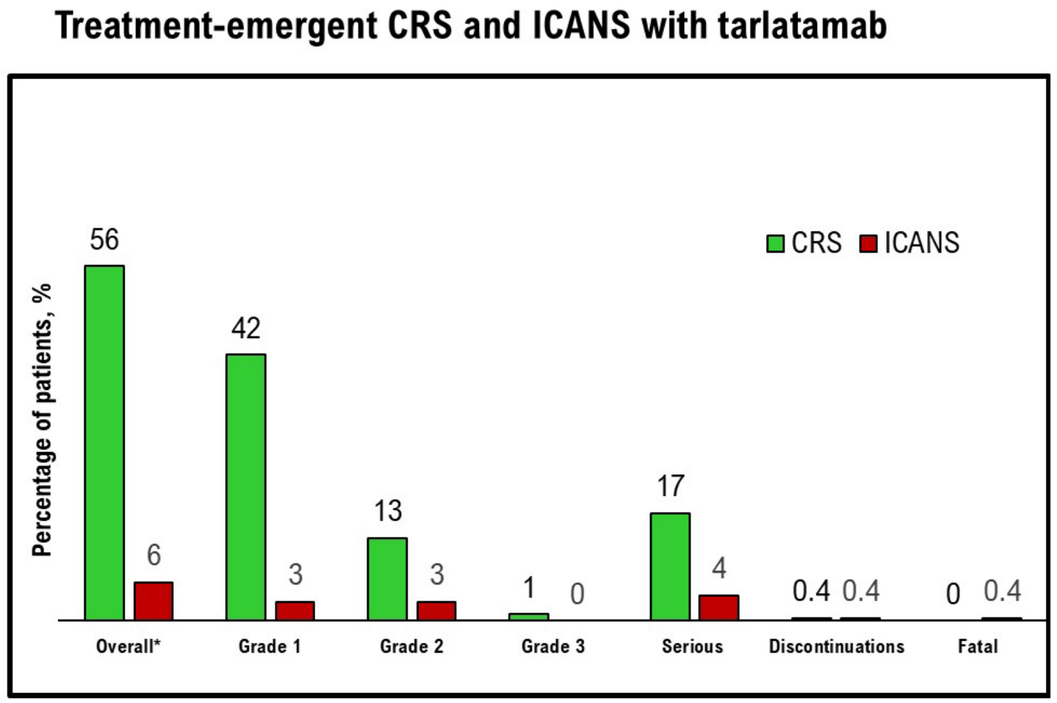


Figure 1. Overall Survival (Intention-to-Treat Population).

Rudin, ASCO Plenary 2025; Mountzios et al, NEJM, 2025

Management: Taralatamab

FDA accelerated approval 05/2024



- Adverse events: 98% were G1/G2 almost exclusively C1 (D1,8,15)
  - CRS: 56% (G3= 1%)
  - ICANS: 6% (G3=0%)
- Common chronic toxicities:
  - Dysgeusia, weight loss, appetite loss, headaches, constipation

Rudin, ASCO Plenary 2025; Mountzios et al, NEJM, 2025

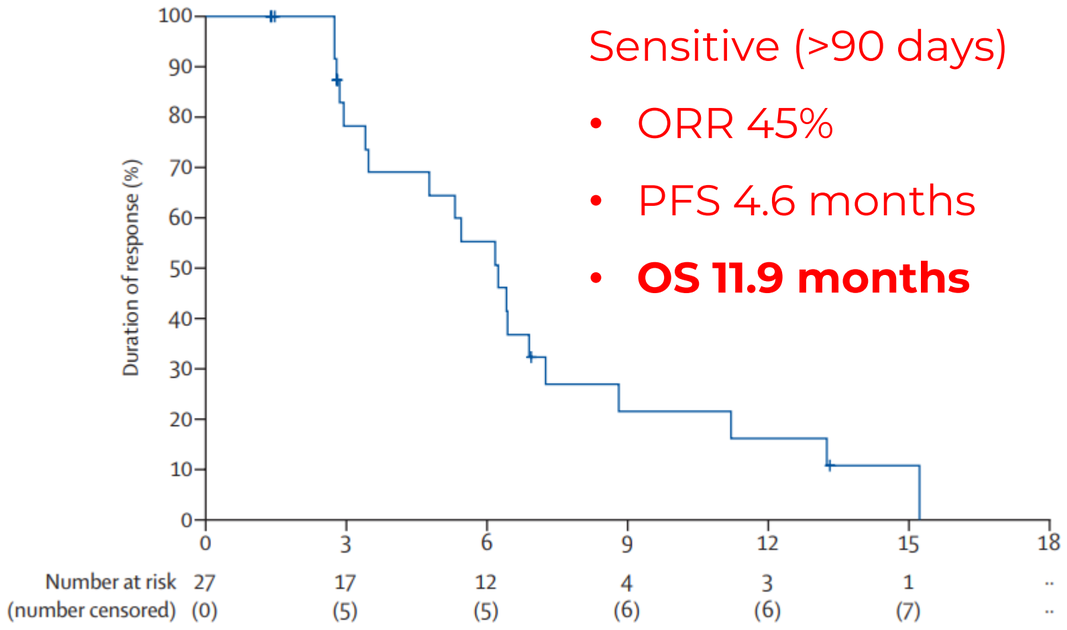
The race continues…

Trial	Phase	Participant criteria	Intervention	Primary Outcome	Status
DeLLphi-306	Phase 3	LS-SCLC with no PD after chemoRT	**Tarla** q2wks IV vs placebo	PFS (by BICR)	Recruiting
RABBIT	Phase 1/2	R/R SCLC or HGNET	**Tarla** IV + concurrent RT vs **Tarla** + sequential RT vs **Tarla**	DLTs	Not yet Recruiting
DeLLphi-305	Phase 3	ES-SCLC with no PD after 1L platinum/etop/durva	Maintenance Durva q4wk IV vs Durva + **Tarla** q2 wk IV	OS	Recruiting
DeLLphi-312	Phase 3	ES-SCLC no prior tx	Carbo/Etop/Durva/**Tarla** IV **>** mDurva/**Tarla** vs Carbo/Etop/Durva>mDurva	OS	Not yet Recruiting
DeLLphi-310	Phase 1b	ES-SCLC with arms for 1L and R/R ES-SCLC	Dose exploration/expansion: YL201 (B7-H3 ADC) + **Tarla** IV Experimental: YL201+ **Tarla** IV + anti-PD-L1	DLTs and TEAEs	Recruiting
Delphi 311	Phase 1b	R/R ES-SCLC	Dose exploration/expansion: AB248 (anti-CD8 Ab/IL2 protein) + **Tarla** IV	DLTs and TEAEs	Not yet Recruiting
Delphi 309	Phase 1b	R/R ES-SCLC	Dose exploration/expansion: **SC tarlatamab**	DLTs, TEAEs, delta VS/Labs	Recruiting
NCT06830694	Phase 2	EGFR mut NSCLC with transformation to SCLC after EGFR TKI	Carbo/Etop/Atezo/**tarlatamab**> **m**Atezo/Tarla	PFS	Not yet Recruiting

Management: Relapse

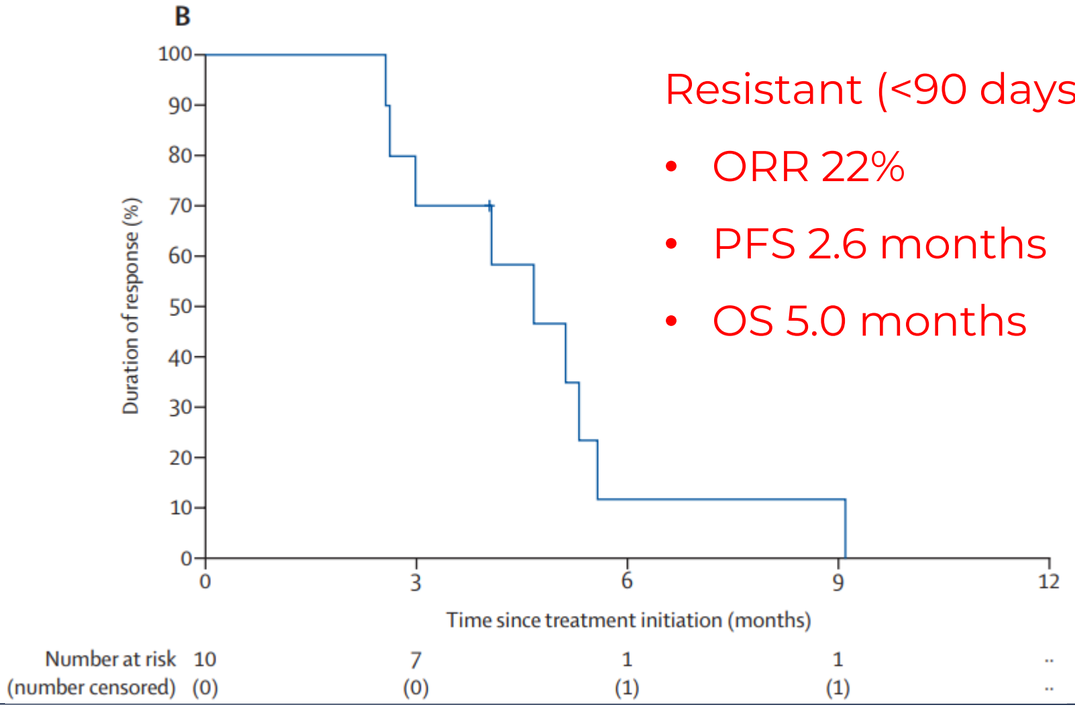
FDA approval 06/2020

- Lurbinectedin: interferes with DNA transcription/repair



Sensitive (>90 days)

- ORR 45%
- PFS 4.6 months
- **OS 11.9 months**

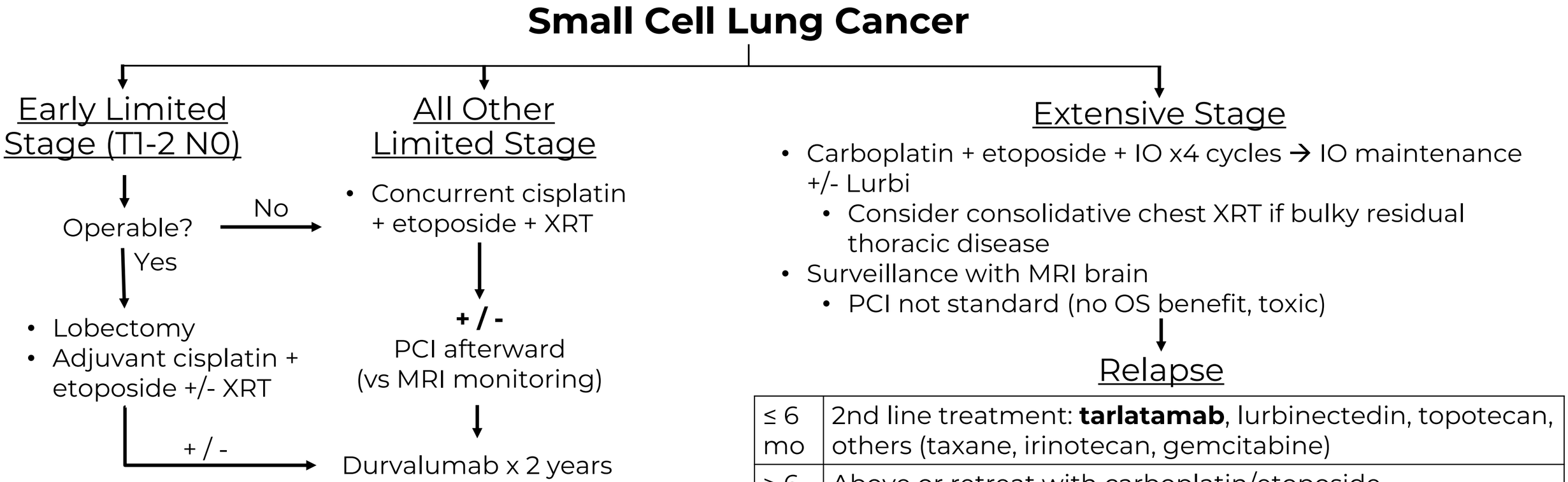


Resistant (<90 days)

- ORR 22%
- PFS 2.6 months
- OS 5.0 months

Trigo J, et al. *Lancet Oncol*. 2020;21(5):645-54.

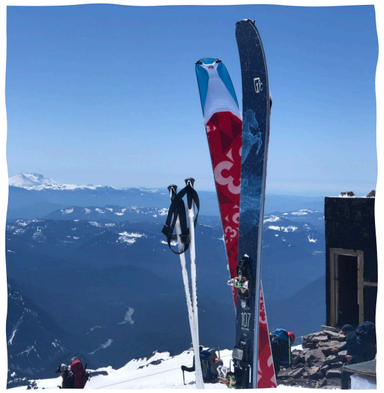
Summary: SCLC Management

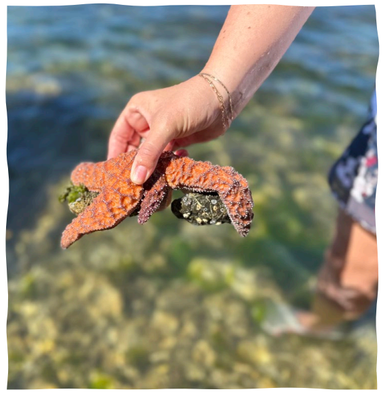


≤ 6 mo	2nd line treatment: **tarlatamab**, lurbinectedin, topotecan, others (taxane, irinotecan, gemcitabine)
> 6 mo	Above or retreat with carboplatin/etoposide

Fred Hutch Cancer Center

Thank you!





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