Small Cell Lung Cancer

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I have no financial conflicts of interest to disclose.

Background & Diagnosis

Background

- 10-15% of lung tumors
- Occurs almost exclusively in smokers
- Rapid growth
- Tends to present as metastatic disease

Clinical Presentation

- Central lung mass with bulky mediastinal adenopathy
  - Metastases: liver, adrenal glands, brain, bone, bone marrow
- Patients often symptomatic
  - Post-obstructive pneumonia
  - SVC syndrome (treat with chemo)
  - Paraneoplastic syndromes

Clinical Presentation: Paraneoplastic Syndromes

Syndrome	Etiology	Presentation
Hyponatremia (SIADH)	Ectopic ADH secretion	Most asymptomatic, ↓ sodium and serum osm, ↑ urine osm
Cushing syndrome	Ectopic ACTH secretion	Hypokalemia, abnormal glucose tolerance, edema, central obesity
Lambert-Eaton myasthenic syndrome (LEMS)	Antibodies against voltage-gated calcium channels → ↓ ACh release from presynaptic nerve terminals	Proximal muscle weakness (temporary improvement with exercise), dry mouth, ptosis

Gandhi L and BE Johnson. *JNCCN*. 2006;4(6):631-38.

Diagnosis: Recommended Work-up

- Labs (BMP, LFTs, CBC)
- Pathology review
- CT chest/abdomen/pelvis with contrast
- MRI brain

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

NCCN Guidelines: Small Cell Lung Cancer. Version 3.2021. https://www.nccn.org/professionals/physician_gls/pdf/sclc.pdf.

Diagnosis: Pathology

- Poorly-differentiated neuroendocrine carcinoma
  - Small round blue cells
  - >10 mitoses/2 mm^2 field
  - IHC:
    - Positive for markers of neuroendocrine differentiation: CD56/NCAM, synaptophysin, chromogranin A (negative in <10%)
    - Positive for TTF-1 (85-90%)
    - Ki-67 50-100%

NCCN Guidelines: Small Cell Lung Cancer. Version 3.2021. https://www.nccn.org/professionals/physician_gls/pdf/sclc.pdf.

Staging

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

Management

Management: Limited-stage SCLC

- T1-2 (tumor <5 cm), N0

  resection → adjuvant cisplatin/etoposide x4 cycles

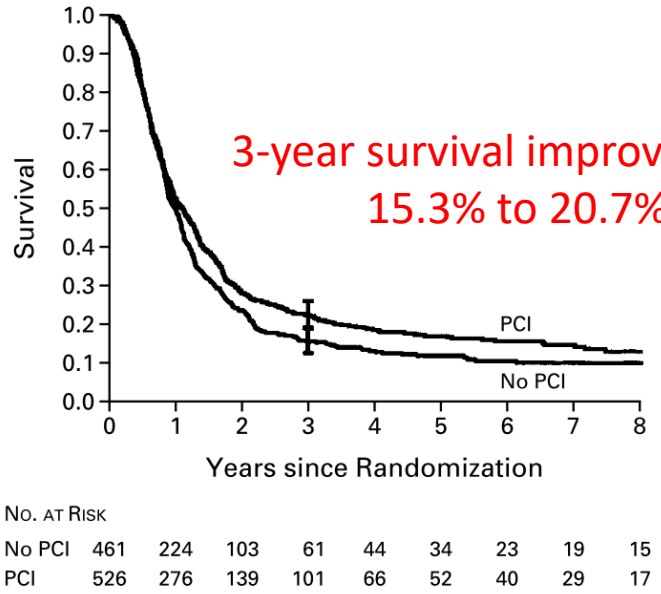
  + XRT (if pN1 or pN2)

- All other limited stage disease

  concurrent cisplatin/etoposide and XRT

Management: Limited-stage SCLC

- After chemoXRT, give prophylactic cranial irradiation (PCI)

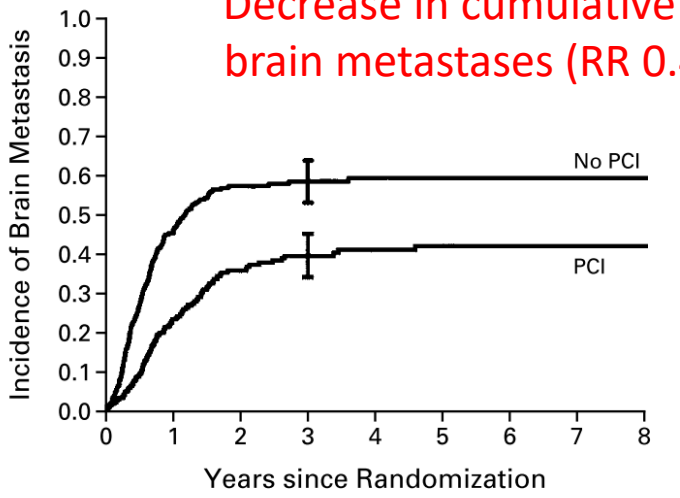


3-year survival improvement:
15.3% to 20.7%

No. at Risk

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

Decrease in cumulative incidence of brain metastases (RR 0.46, p<0.001)



No. at Risk

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

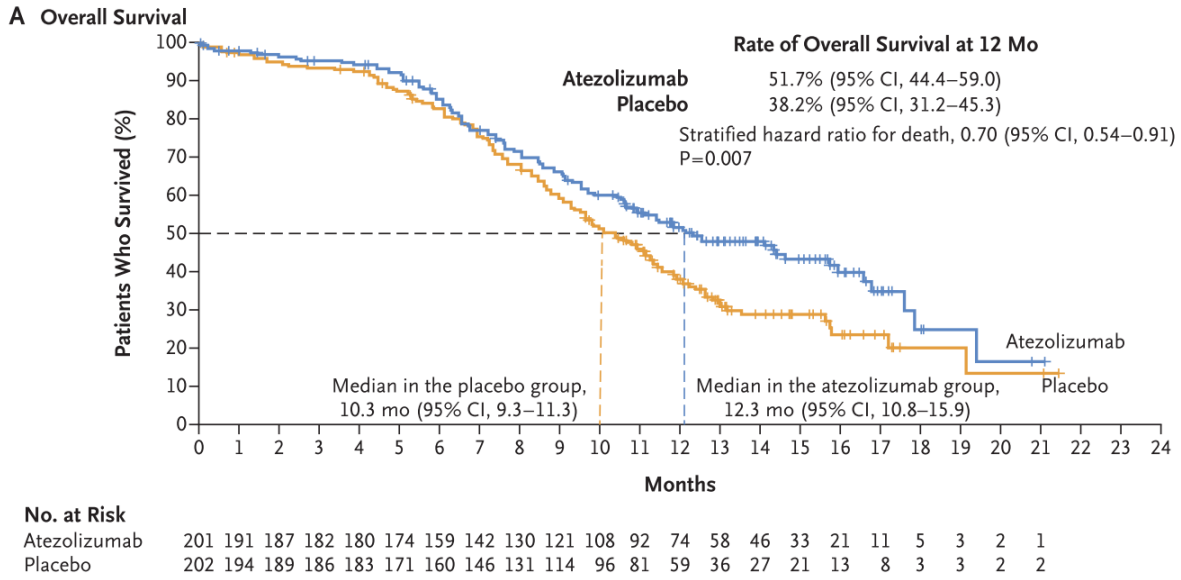
Auperin A, et al. *NEJM*. 1999;341:476-84.

Management: Extensive-stage SCLC

- Deciding when to start treatment is challenging
- New first-line standard of care: chemotherapy + immunotherapy (IO)

Management: Extensive-stage SCLC

- Carboplatin/etoposide + IO x4 cycles → IO maintenance
  - IO: atezolizumab or durvalumab currently FDA approved

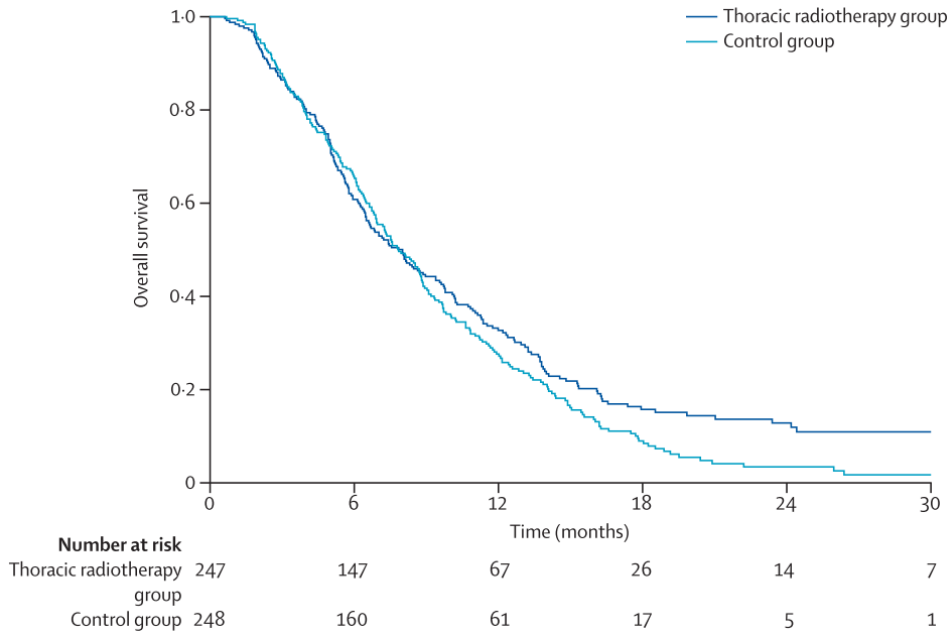


- 2 month improvement in OS
- 1 month improvement in PFS
- Similar ORR (roughly 60%)
- Adverse effect profile similar

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

Management: Extensive-stage SCLC

- Can consider consolidative thoracic XRT in select patients after chemo
  - Responsive disease, no brain mets (MRI not required), ECOG 0-2

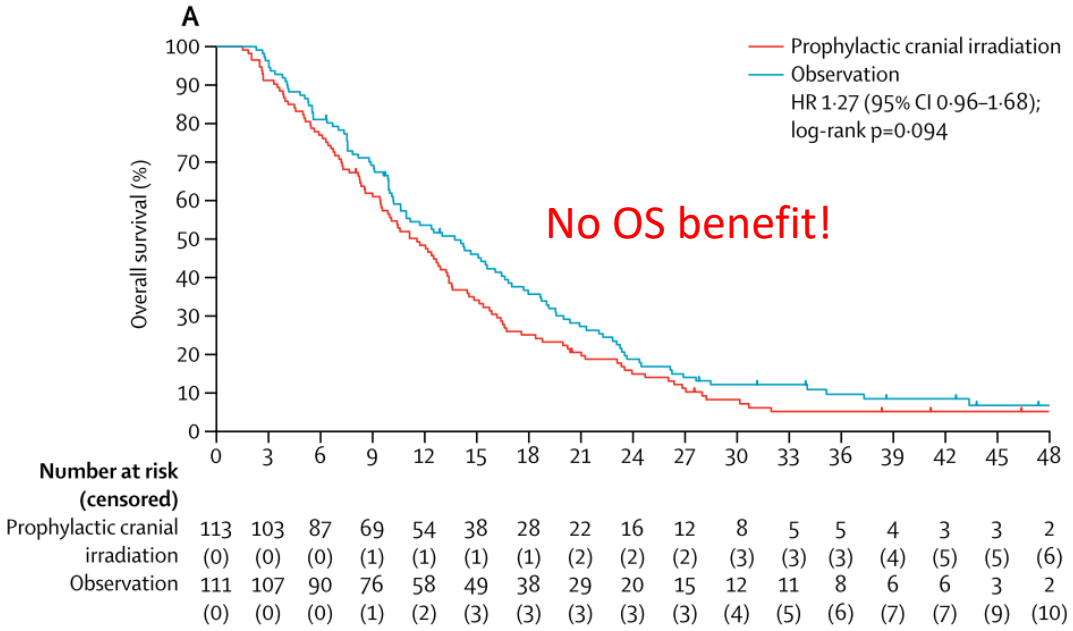


- OS benefit not until 2 years (13% vs 3%)
- PFS benefit starting at 6 months
- 50% reduction in intrathoracic recurrences

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

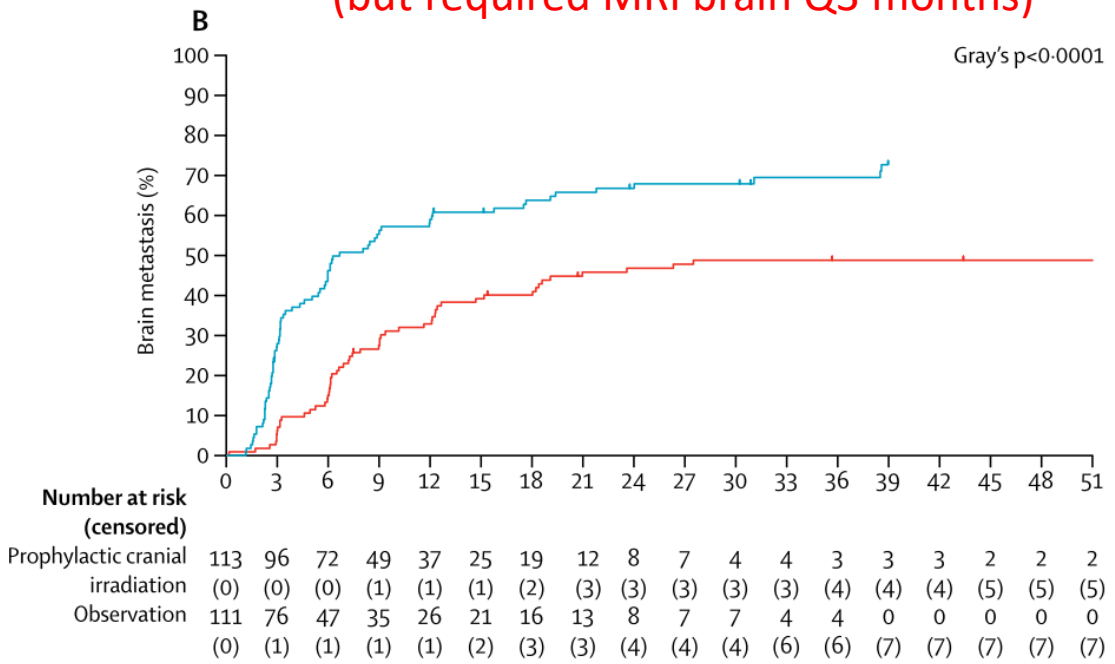
Management: Extensive-stage SCLC

- PCI no longer standard → surveillance with MRI brain



No OS benefit!

Lower frequency of brain mets
(but required MRI brain Q3 months)



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

Management: Extensive-stage SCLC

All data on consolidative thoracic radiation and PCI collected prior to new standard of care → unclear what to do with IO

Management: Relapse

- Therapy depends on timing of relapse

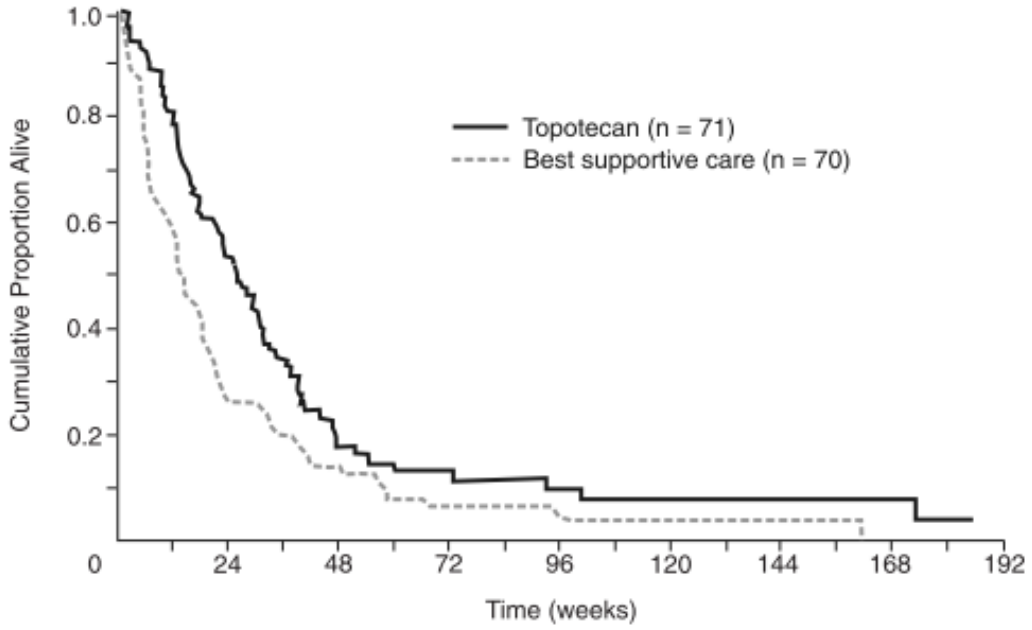
Management: Relapse

- ≤ 6 months: second line treatment
  - Lurbinectedin(*)
  - Topotecan*
  - Taxane
  - Irinotecan
  - Gemcitabine
  - Can consider pembrolizumab monotherapy *or* nivolumab +/- ipilimumab if no previous IO

*FDA approved for second line+

Management: Relapse

- Topotecan: topoisomerase I inhibitor
  - IV or PO
  - No symptomatic CNS metastases

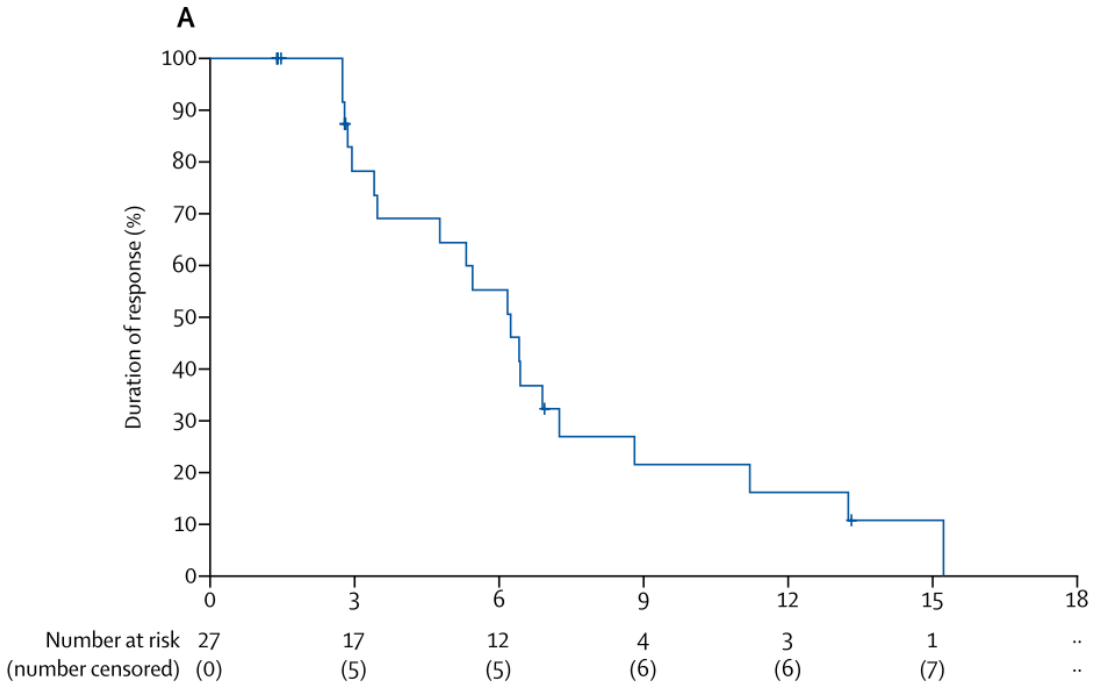


- ORR 7% (additional 44% with disease stabilization)
- Median OS ~6.5 months
- Major AE: hematologic

O'Brien MER, et al. *J Clin Oncol*. 2006;24:5441-47.

Management: Relapse

- Lurbinectedin: selective transcription inhibitor
  - No CNS metastases

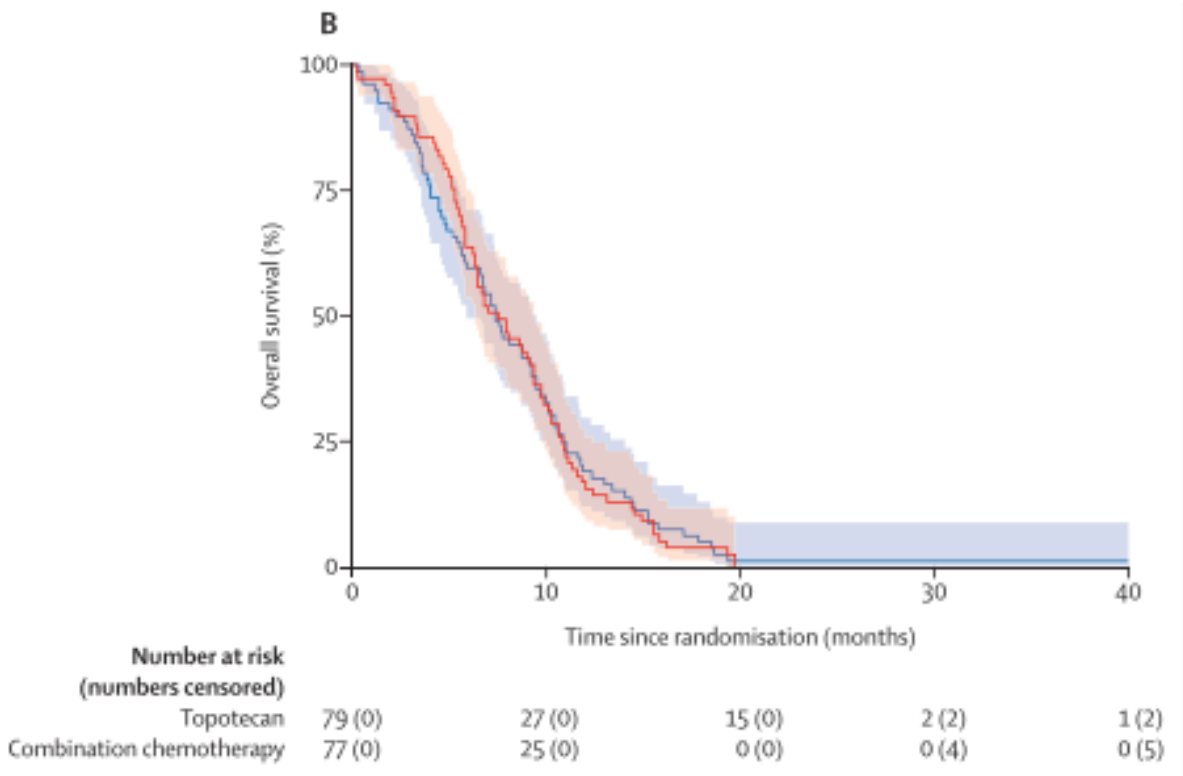


- ORR 35%
- Median PFS 3.5 months
- Median OS 9.3 months
- Major AE: hematologic

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

Management: Relapse

- > 3-6 months: carboplatin/etoposide rechallenge



- ORR improvement (49% vs 25%)
- Median PFS improvement (4.7 vs 2.7 months)
- Median OS similar (roughly 7.5 months)

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

Summary: SCLC Management

SCLC

Limited Stage

T1-2 N0	resection → adjuvant cisplatin/etoposide x4 cycles +/- XRT
All other	concurrent cisplatin/etoposide + XRT

+

PCI afterward (for all)

Extensive Stage

- Carboplatin/etoposide +/- IO x4 cycles → IO maintenance
  - Consider consolidative chest XRT if bulky residual thoracic disease
- Surveillance with MRI brain
  - PCI no longer standard (no OS benefit, toxic)

Relapse

≤ 6 mo.	second line treatment (lurbinectedin, topotecan, taxane, irinotecan, gemcitabine)* *Can consider nivolumab +/- ipilimumab or pembrolizumab monotherapy if no previous IO
> 6 mo.	retreat with carboplatin/etoposide

Question #1

Which of the following is TRUE regarding management of limited stage small cell lung cancer?

a) Prophylactic cranial irradiation should be offered to all patients after completion of chemoradiation.

b) Mediastinal staging is recommended for patients with tumors <7 cm and clinically node negative.

c) There is never a role for resection of limited stage small cell lung cancer.

d) Patients can have limited stage disease even if a pleural effusion is present.

Explanation: Prophylactic cranial irradiation should be offered to all patients with limited stage small cell lung cancer given a demonstrated overall survival benefit and decreased incidence of brain metastases. Answer (b) is incorrect, as mediastinal staging should be considered for tumors <5 cm and clinically node negative. Answer (c) is incorrect because resection is considered for T1-2 (tumor <5 cm) N0 disease. The presence of a pleural effusion is consistent with extensive stage disease, making answer (d) incorrect.

Question #2

A 56 year-old female patient with extensive stage small cell lung cancer presents to your office. She completed 4 cycles of carboplatin/etoposide/durvalumab with good treatment response, and has now been on maintenance durvalumab for 2 months. Unfortunately, her restaging CT scan shows worsening mediastinal lymphadenopathy and new osseous metastases. She has a good performance status, no significant laboratory abnormalities, and would like to continue receiving treatment. All of the following would be a reasonable next step, EXCEPT:

a) Lurbinectedin

b) Topotecan

c) Carboplatin/etoposide

d) Paclitaxel

Explanation: Carboplatin/etoposide rechallenge (answer c) is not recommended because your patient has experienced disease progression at <6 months from prior carboplatin/etoposide exposure. Lurbinectedin, topotecan or paclitaxel would all be reasonable second line treatment options, although only the first two are FDA approved for this indication.