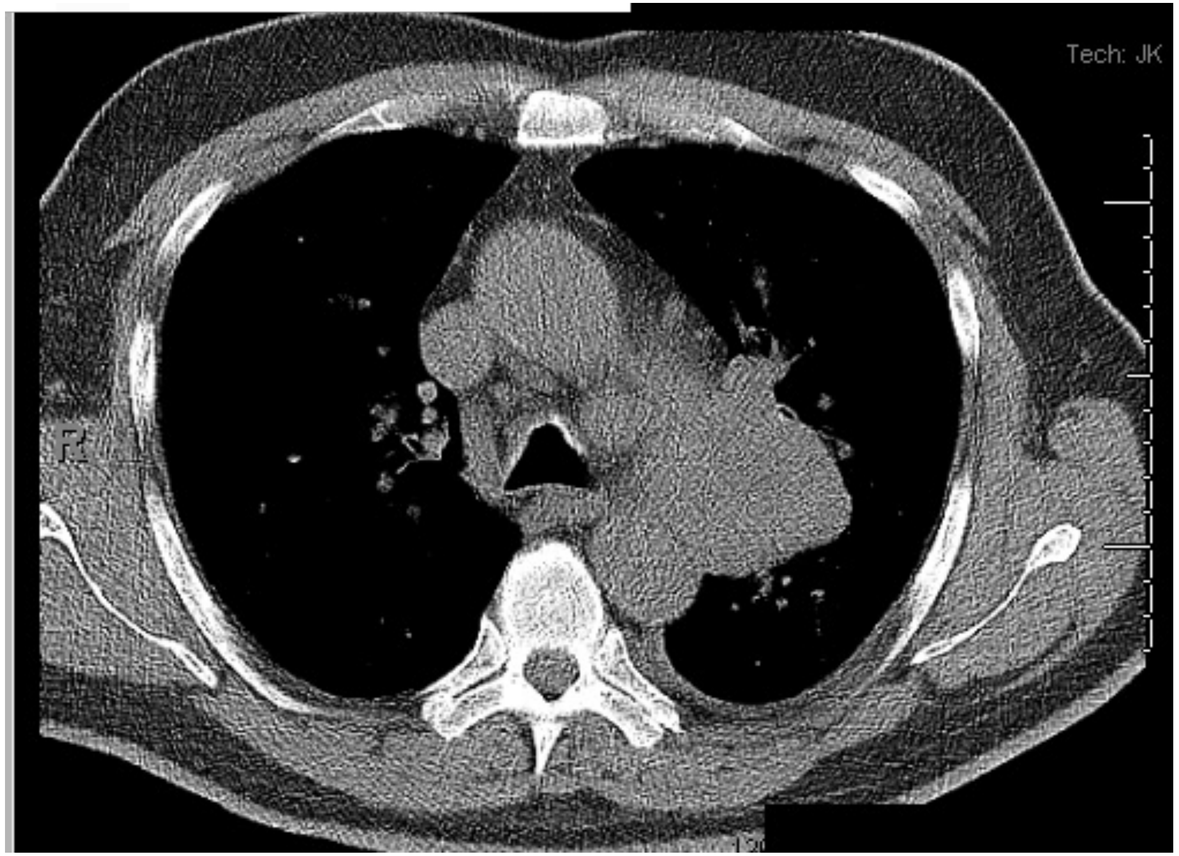
Small Cell Lung Cancer case

J. Marie Suga, MD/MPH
National Kaiser Permanente Lung Cancer Chair
Principal Investigator, Kaiser Permanente NCORP

KAISER PERMANENTE®

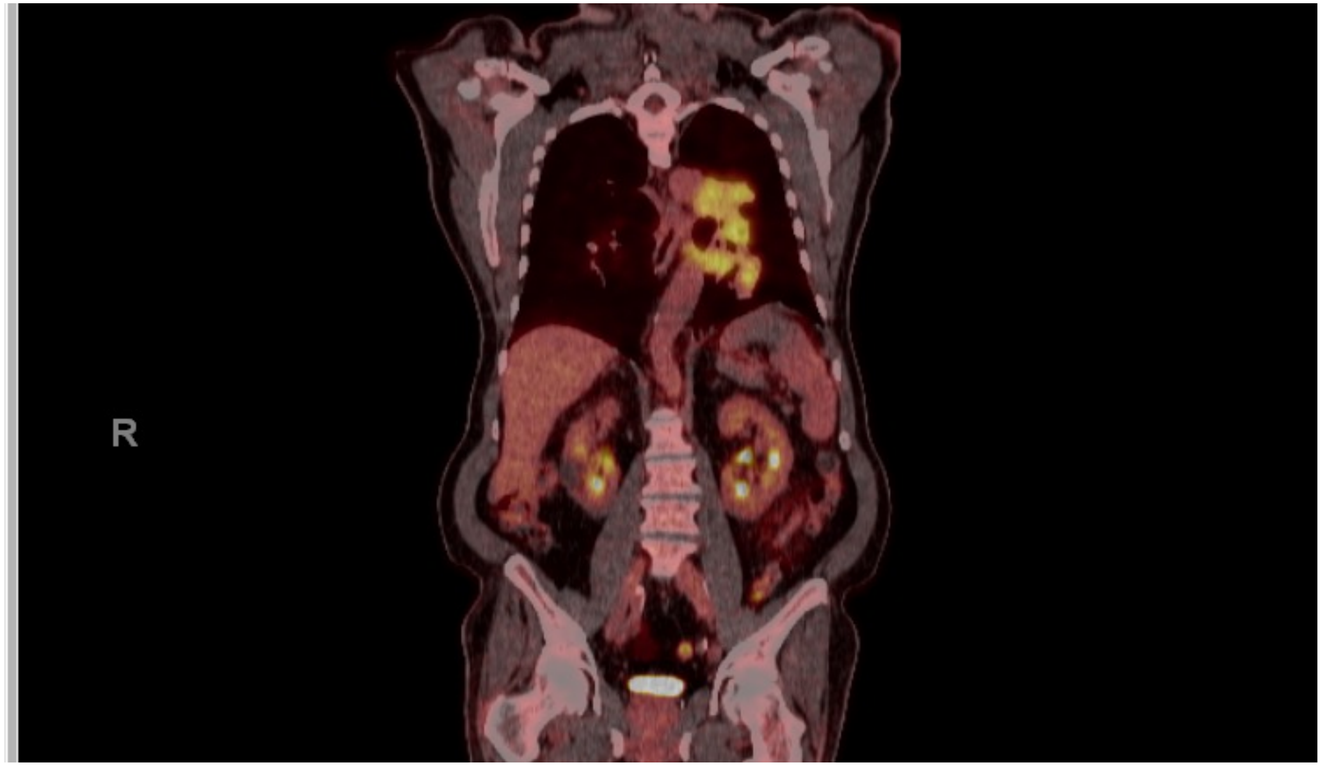
SCLC case:

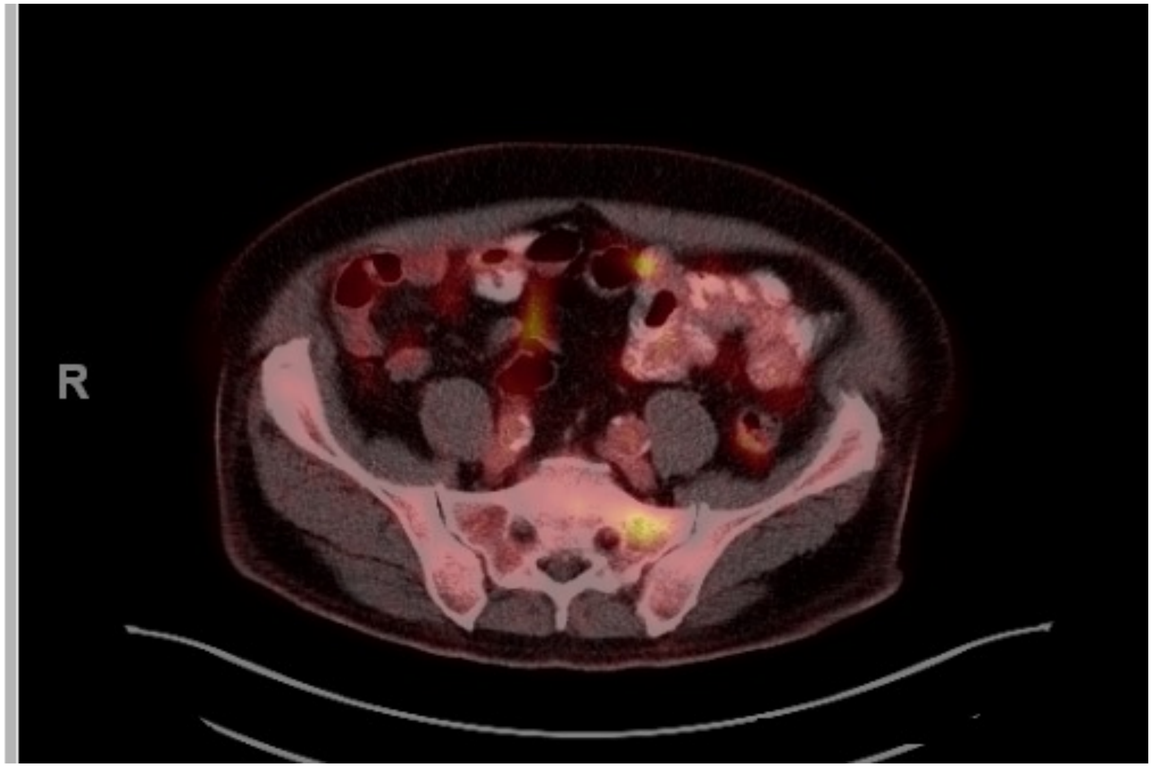
68 year old man, current smoker (40 packyear), who was vacationing on the east coast, went to the ER with acute shortness of breath. PS=0. CT scan showed a large soft tissue mass in the left mediastinum which encases the left pulmonary artery, extending to perihilar region, small left pleural effusion.



SCLC case continued:

- PET scan showed large conglomerate mass in Left Lower Lobe, left hilum, mediastinum, and left sacral metastasis
- EBUS-directed biospy of the left paratracheal LN was positive for small cell lung cancer
- MRI brain negative for cancer



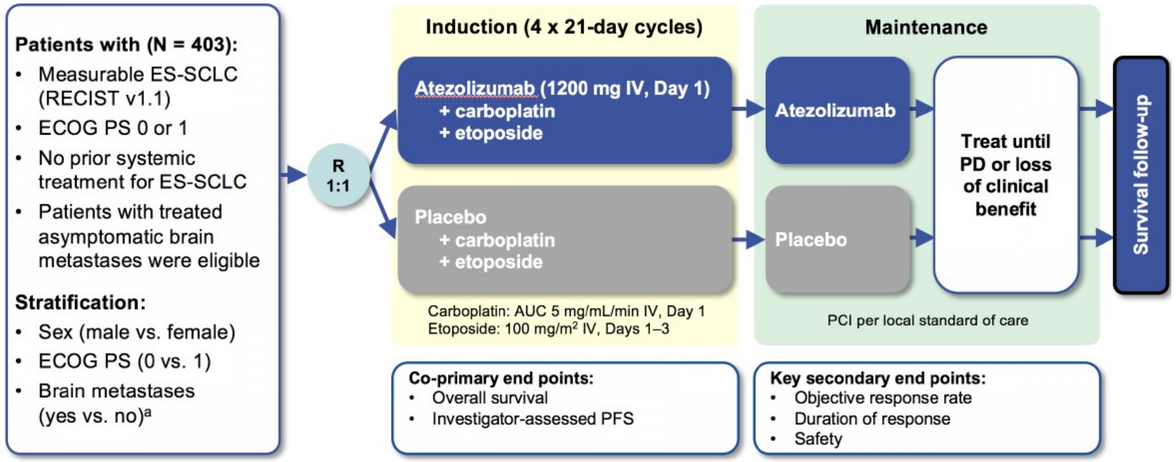


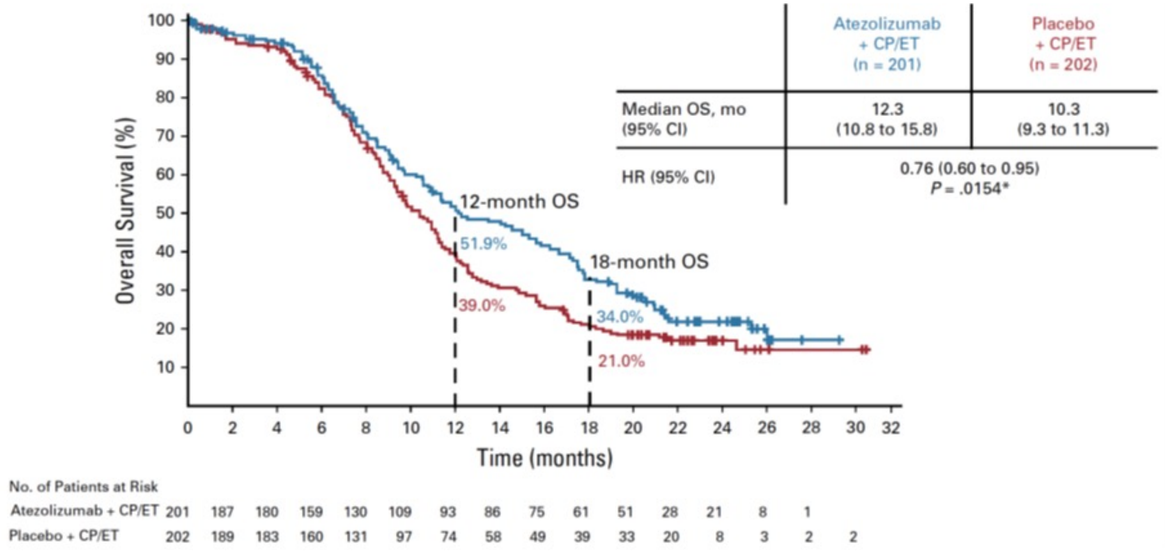
SCLC case continued:

- For this 68 year old man with newly diagnosed metastatic small cell lung cancer with a PS =0 , what would be the best recommended first line of treatment:

1) Carboplatin/etoposide/pembrolizumab
2) Carboplatin/etoposide/atezolizumab
3) Cisplatin/etoposide/durvalumab/tremelimumab
4) Carboplatin/etoposide

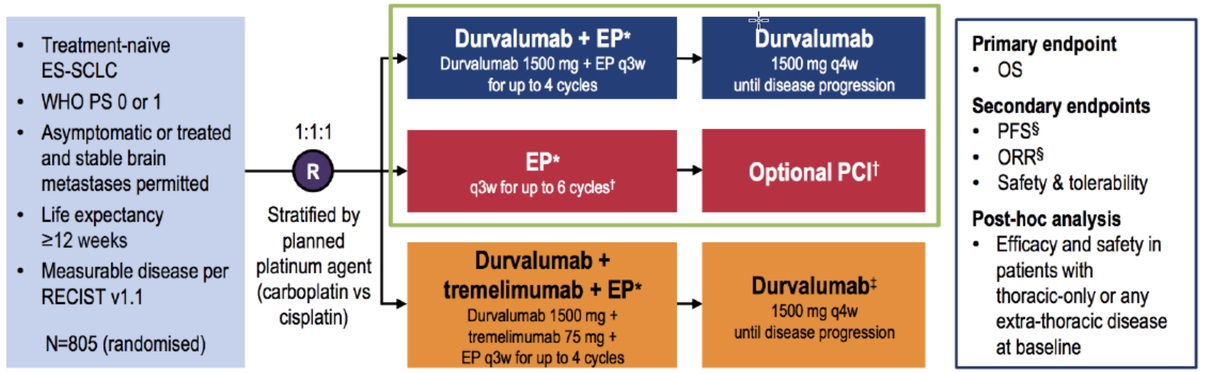
IMpower 133

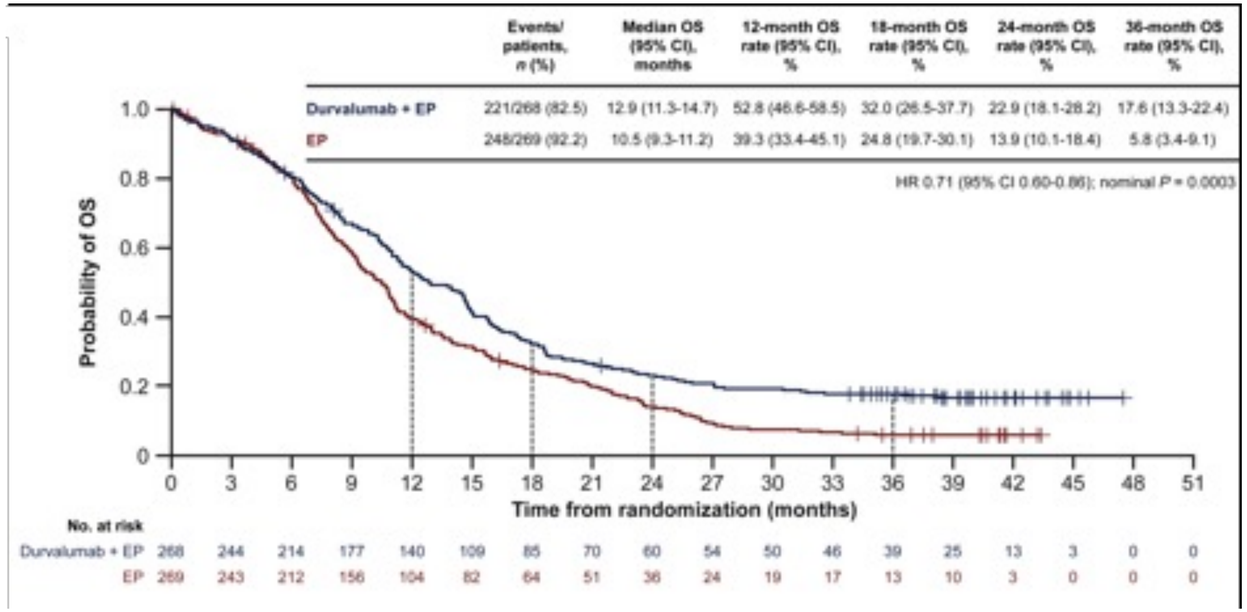




Liu, JCO 2021

CASPIAN





Paz-Ares, ESMO Open 2022

FDA Approval for 1L ES-SCLC

	IMpower133 updated analysis	CASPIAN updated analysis
Median follow up	22.9 mo	39.4 mo
mOS	12.3 vs 10.3 mo	12.9 vs 10.5 mon
HR	0.76, p=0.0154	0.71, p=0.0003
1YOS	51.9 vs 39%	52.8 vs 39.3%
2YOS	22 vs 17%	22.9 vs 13.9%
3YOS		17.6 vs 5.8%
Eligibility	Treated brain mets only	Asymptomatic brain mets allowed
Chemo	Carboplatin	Cis or carboplatin

IMpower 133 irAE rates

BARCELONA 2019 ESMO congress

Adverse events of special interest

Immune-related AEs[a], n (%) > 1% in either treatment group	Atezo + CP/ET (n = 198)		Placebo + CP/ET (n = 196)	
	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
Rash	36 (18.2)	4 (2.0)	21 (10.7)	0
Hepatitis	12 (6.1)	3 (1.5)	9 (4.6)	0
Hypothyroidism	25 (12.6)	0	1 (0.5)	0
Hyperthyroidism	11 (5.6)	0	5 (2.6)	0
Infusion-related reaction	7 (3.5)	4 (2.0)	9 (4.6)	1 (0.5)
Pneumonitis	4 (2.0)	1 (0.5)	3 (1.5)	2 (1.0)
Colitis	1 (0.5)	2 (1.0)	0	0
Adrenal insufficiency	0	0	3 (1.5)	0

- No grade 5 immune-related AEs were observed in either treatment group

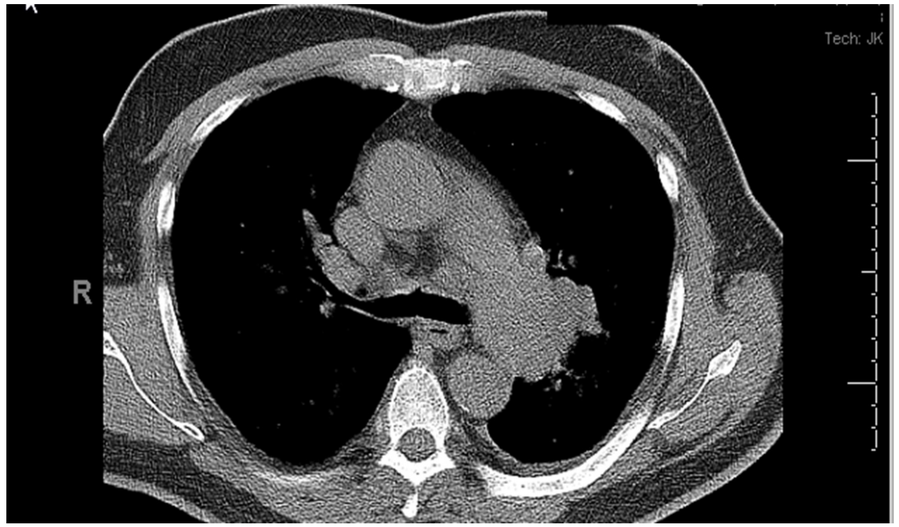
[a] An event consistent with an immune-mediated mechanism of action not taking into account whether treatment given for the event.
CCOD 24 January 2019

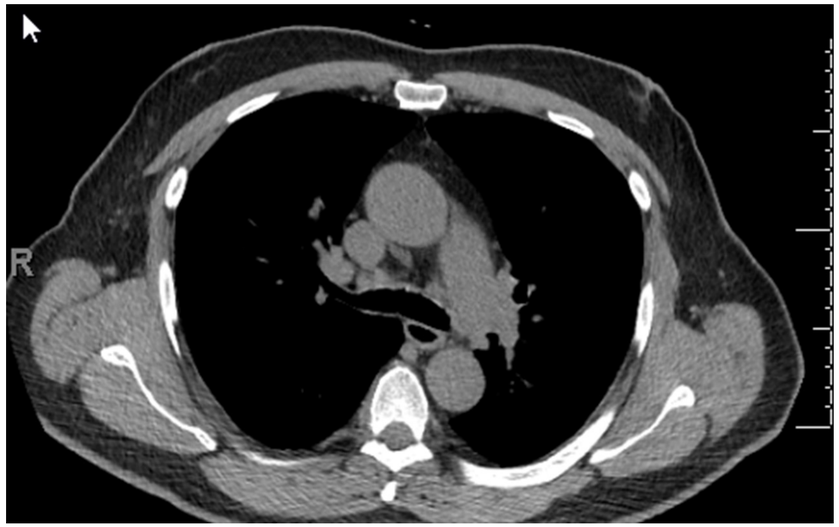
IMpower133 Updated OS Analysis: presented by Dr Martin Reck

http://bit.ly/2Z32WhW

SCLC case continued

- Patient received 4 cycles of carboplatin/etoposide/atezolizumab and achieves a very good partial response

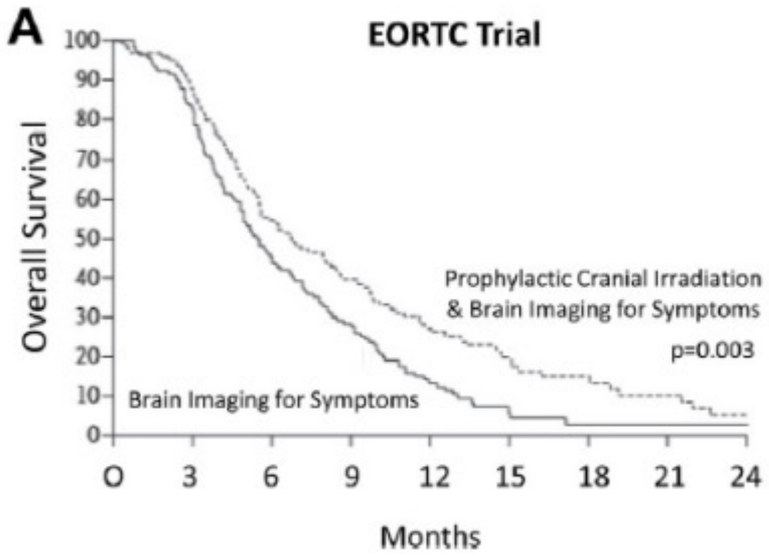




- What would you recommend next?

1) Observation
2) Start maintenance atezolizumab
3) Referral to Radiation Oncology for PCI and start maintenance Atezolizumab

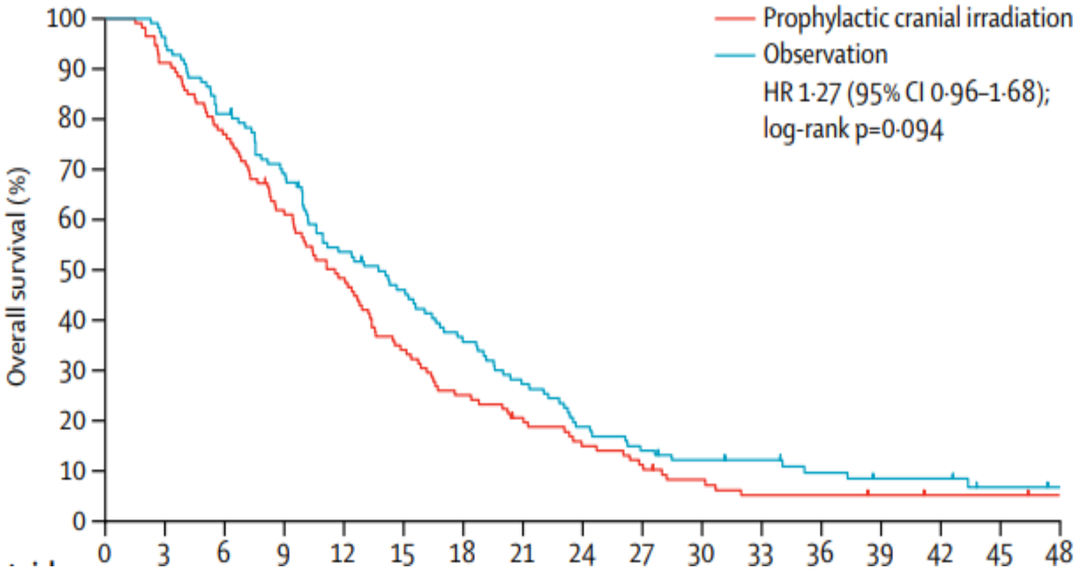
Prophylactic Cranial Irradiation (PCI) for ES-SCLC



Slotman, NEJM 357.7 (2007): 664-672

1-year OS was 27.1% PCI vs 13.3% no PCI

Overall Survival



Takahashi, Lancet Oncol 18.5 (2017): 663-671

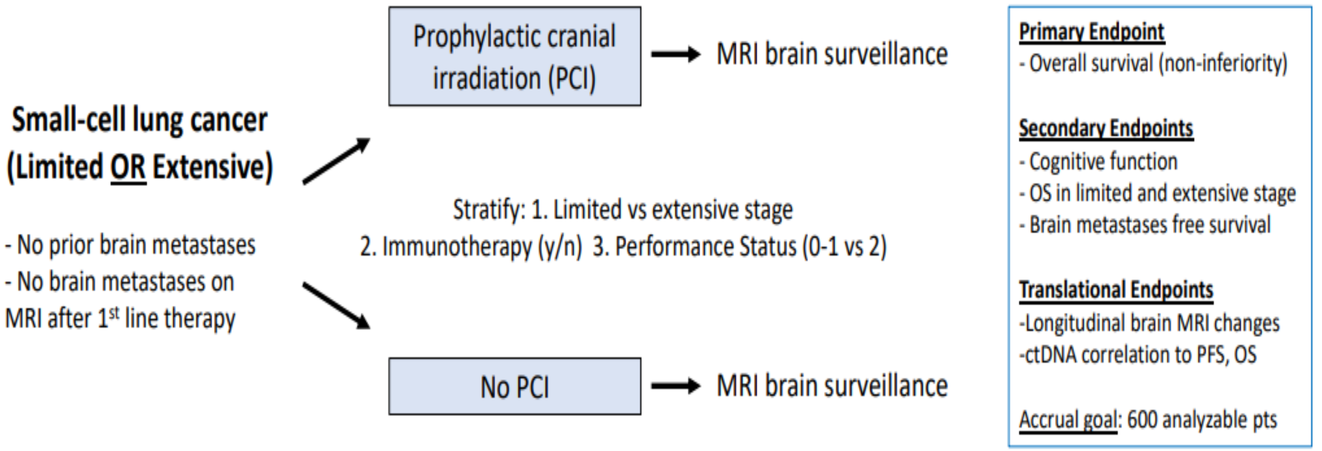
no differences in PFS or OS with the addition of PCI (median OS 13.7 vs 11.6 mo, p=0.09, favoring no-PCI)

Ongoing Radiation PCI Trial for SCLC

PCI for SCLC

MAVERICK (SWOG 1827)

MRI Brain Surveillance Alone Versus MRI Surveillance and Prophylactic Cranial Irradiation: A Randomized Phase III Trial in Small-Cell Lung Cancer



Study Chair: Rusthoven

SCLC case continued

- Patient continues with atezolizumab maintenance

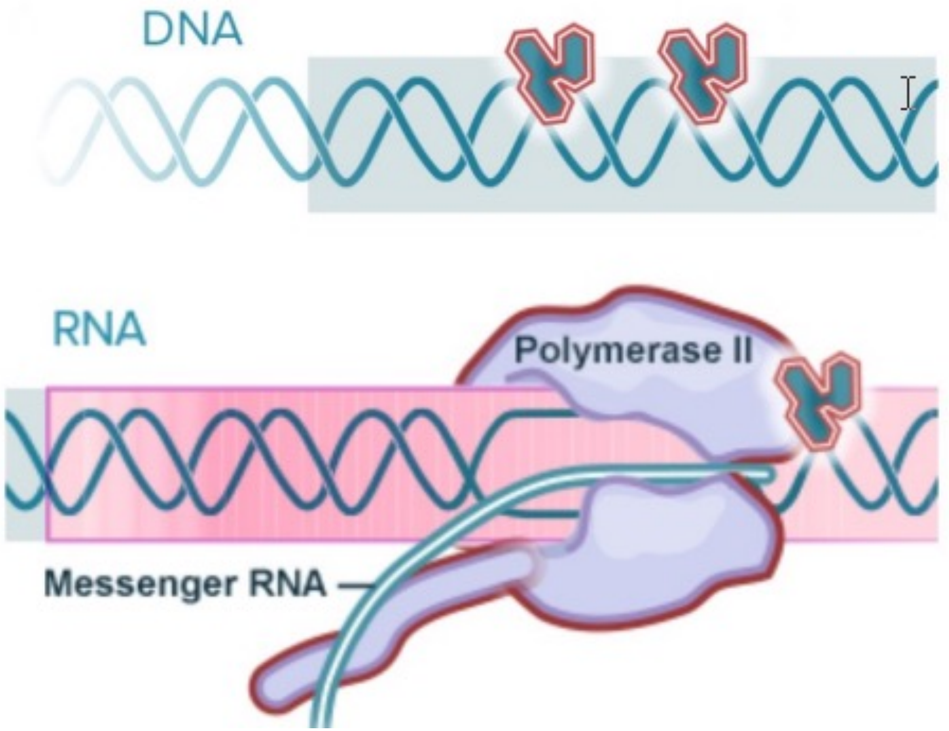
- After 12 months of maintenance atezolizumab, patient has systemic disease progression

What would be your next recommendation for this patient?

1) Lurbinectedin
2) Rechallenge with carboplatin/etoposide
3) Topotecan
4) Nivolumab

Lurbinectedin Mechanism of Action

Effects on the tumor



- Binds to guanine residues in the minor groove of DNA
- Affects activity of transcription factors

- Stalls RNA polymerase II
- Affects DNA repair pathways
- Results in eventual cell death

Lurbinectedin

- Granted accelerated approval on June 15, 2020

- Single arm open label Phase II trial PM1183-B-005-14 trial, N=105
- ORR=35%, DCR 68%, mDOR=5.3 months
- mPFS=3.5 months; 6 month PFS 33%
- mOS=9.3 months, 6 month OS=67%; 12 month OS=34%

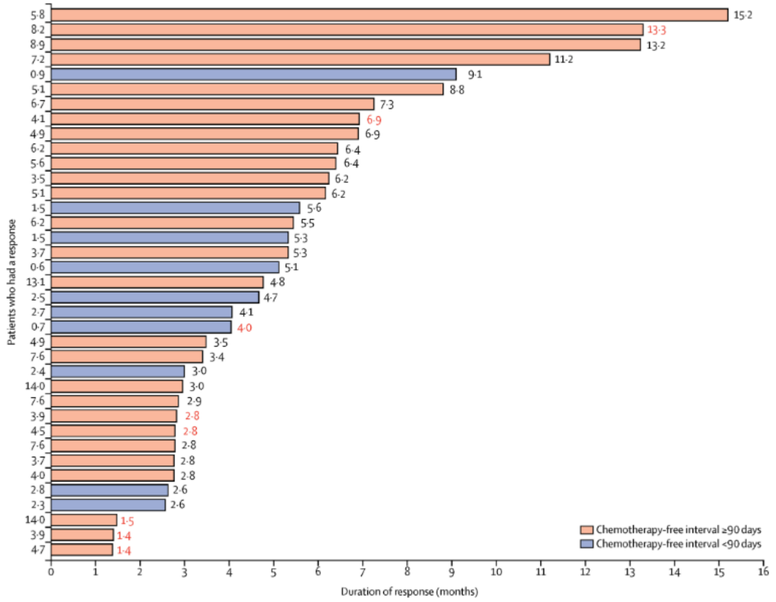


Figure 1
Duration of response by investigator assessment

Trigo, Lancet Oncol 5/2020

Adverse events from lurbinectedin

	Grade 1–2	Grade 3	Grade 4
Haematological abnormalities (regardless of relation to study drug)*			
Anaemia	91 (87%)	9 (9%)	0
Leucopenia	53 (50%)	20 (19%)	10 (10%)
Neutropenia	27 (26%)	22 (21%)	26 (25%)
Thrombocytopenia	39 (37%)	3 (3%)	4 (4%)
Biochemical abnormalities (regardless of relation to study drug)*			
Creatinine†	86/104 (83%)	0	0
Alanine aminotransferase	69/103 (67%)	5/103 (5%)	0
γ-glutamyl transferase	52/103 (50%)	13/103 (13%)	2/103 (2%)
Aspartate aminotransferase	44/103 (43%)	2/103 (2%)	0
Alkaline phosphatase	31/103 (30%)	3/103 (3%)	0
Treatment-related adverse events			
Fatigue	54 (51%)	7 (7%)	0
Nausea	34 (32%)	0	0
Decreased appetite	22 (21%)	0	0
Vomiting	19 (18%)	0	0
Diarrhoea	13 (14%)	1 (1%)	0
Febrile neutropenia	0	2 (2%)	3 (3%)
Pneumonia	0	2 (2%)	0
Skin ulcer	0	1 (1%)	0

Data are n (%) of patients. NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. *Based on all patients with laboratory data available. †Version 4.0 of NCI-CTCAE grades any creatinine increases from baseline as abnormalities, even if creatinine values remain within the normal range.

Table 3: Most common NCI-CTCAE laboratory abnormalities and treatment-related adverse events

- **Notable adverse events**
  - Myelosuppression
  - Elevated Cr
  - Elevated LFTs
  - Fatigue

Trigo et al., *Lancet Oncol.* 2020

Phase III Atlantis Trial

ATLANTIS: Study Design

- Multicenter, randomized phase III trial

Stratified by ECOG PS (0 vs 1-2), CTFI (≥180 vs 90-179 vs <90 days), CNS involvement (yes vs no), prior PD-1/PD-L1 inhibitor (yes vs no), investigator preference for control arm

Patients with SCLC with 1 prior line of chemotherapy (other biologic lines allowed); ECOG PS 0-2; patients with CTFI <30 days excluded (N = 613)

Doxorubicin* 40 mg/m^2 Day 1 + **Lurbinectedin**† 2 mg/m^2 Day 1 Q3W **(n = 307)**

Topotecan 1.5 mg/m^2 Days 1-5 Q3W or **CAV*** Day 1 Q3W **(n = 306)**

PD or unacceptable toxicity

*Maximum 10 cycles of doxorubicin.
†Lurbinectedin continued as maintenance at 3.2 mg/m^2 Day 1 Q3W.
G-CSF prophylaxis mandatory in both arms.

- **Primary endpoint:** OS
- **Secondary endpoints:** PFS, tumor response, DoR, safety

Paz-Ares. WCLC 2021. Abstr PL02.03.

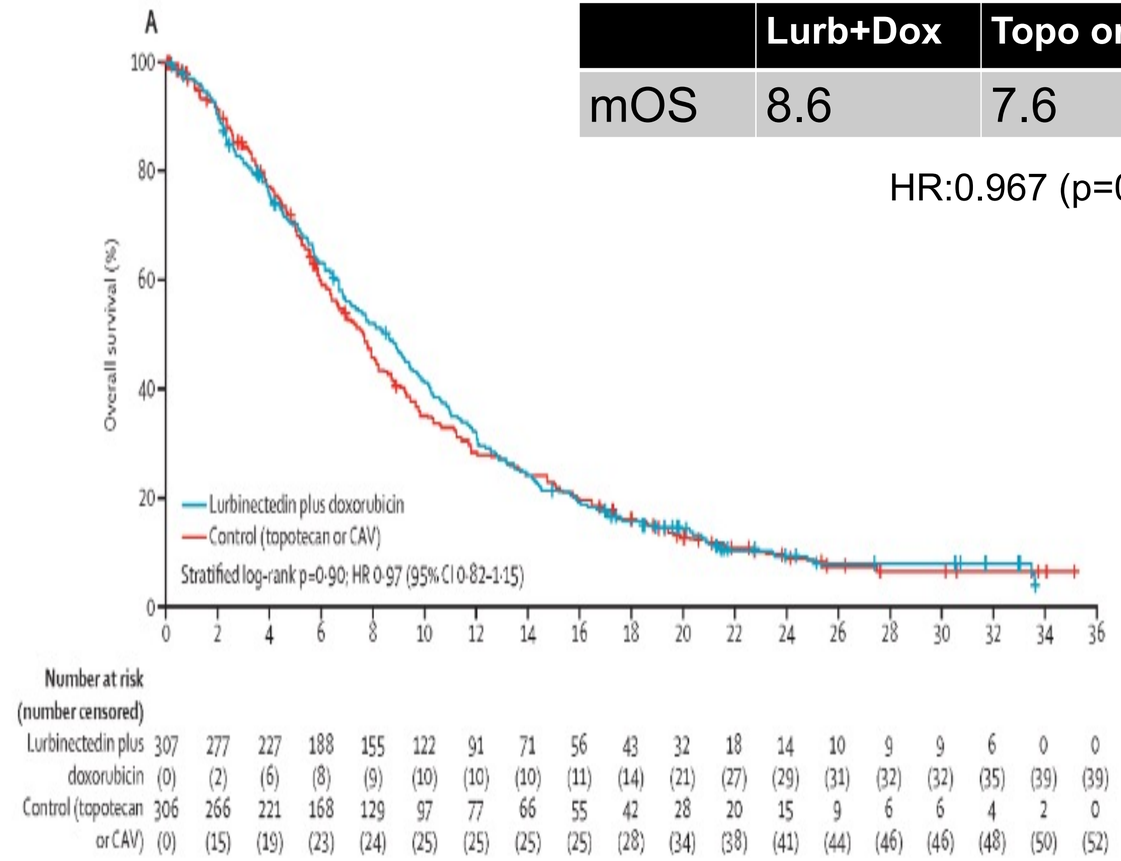
Slide credit: clinicaloptions.com

Overall Survival in ITT

¶ Lurbinectedin plus doxorubicin, n=97; control (topotecan or CAV), n=91.

	Lurb+Dox	Topo or CAV
mOS	8.6	7.6

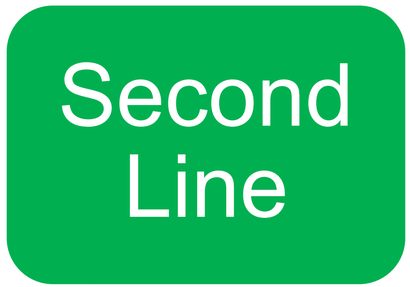
HR:0.967 (p=0.7)



Aix, Lancet resp Oct 2022

Current ES-SCLC Management

- **Platinum/Etoposide + Atezolizumab or Durvalumab →Maintenance immunotherapy**
- **If CR or PR, consider Radiation (Brain PCI or Thoracic radiation)**



- **Relapse <=6 months**
- **Topotecan**
- **Lurbinectedin**
- **Clinical Trial**
- **Consider Reinduction with doublet if relapse between 3-6 months**

Relapse >6 months

- **Reinduction with initial doublet**
- **Topotecan**
- **Lurbinectedin**
- **Clinical Trial**

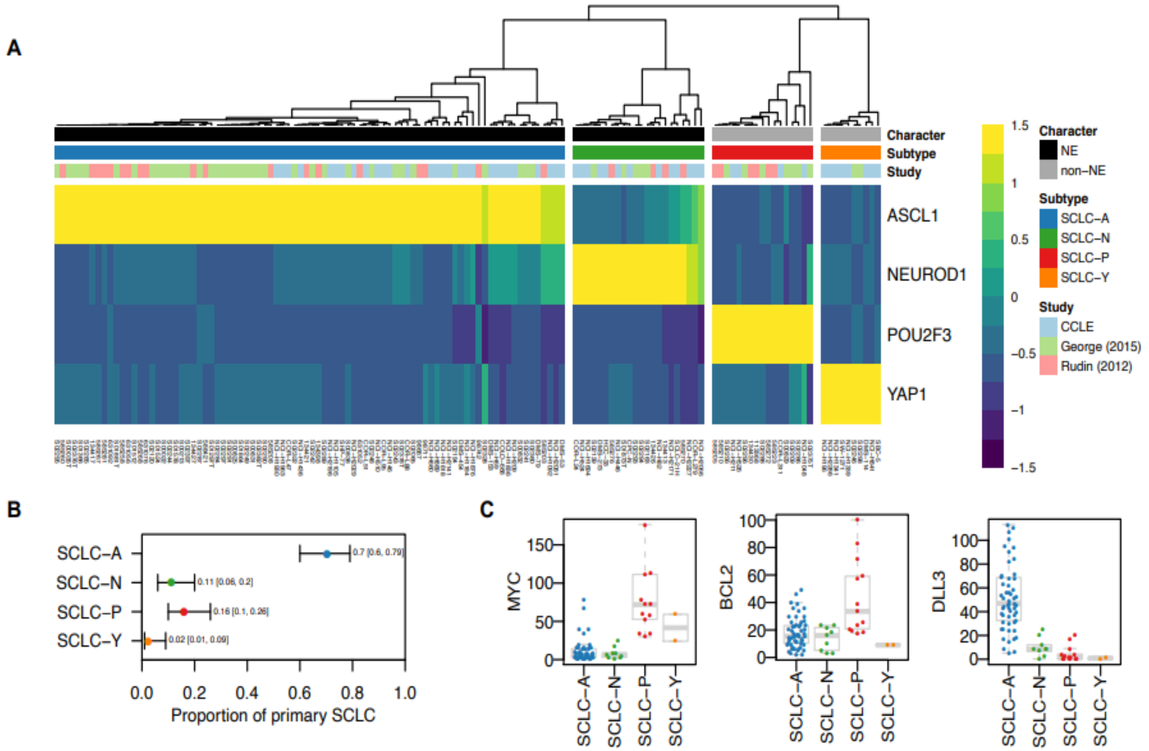
- **Depends on prior regimens, response, patient PS**
- **Topotecan, Lurbinectedin**
- **Other regimens:Taxanes, Irinotecan, CAV**
- **Clinical Trial**

Adapted from NCCN guidelines v 2.2023

Future Directions in SCLC research:

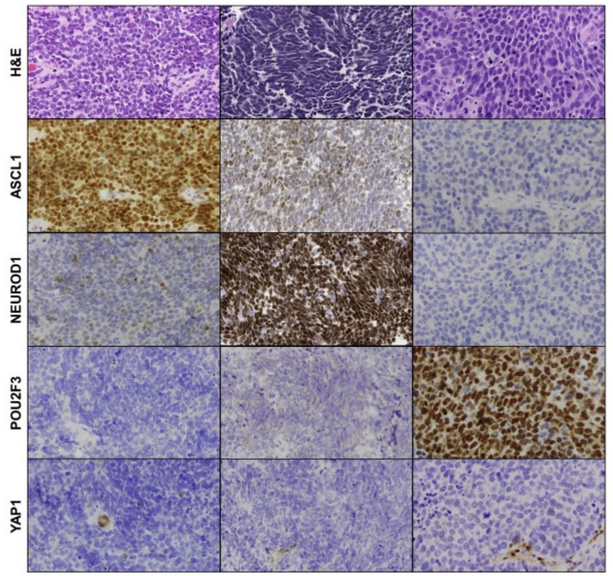
SCLC Subtyping – SCLC-A, N, P, or Y/I

Subtypes of SCLC defined by a dominant transcriptional regulator



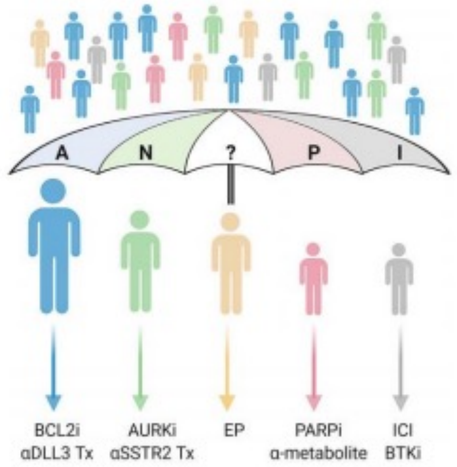
Rudin et al., *Nat Rev Cancer* 2019

Subtype determination – feasible at protein level



Baine et al., *J Thor Oncol* 2020

Subtypes may predict sensitivity to particular agents



Frese, Cancer Cell March 2021

Take Home Messages

- First line metastatic SCLC is platinum doublet + immunotherapy (atezolizumab or durvalumab) followed by maintenance IO until progression
- Second line options are dependent on the clinical scenario and options could include Lurbinectedin, Topotecan, re-induction platinum doublet
- PCI for ES-SCLC is still controversial, many questions still remain
- Research is ongoing to determine whether additional SCLC subtyping can optimize personalized SCLC treatment options for our patients