Small Cell Lung Cancer. The basics

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SCCA

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Small Cell Lung Cancer

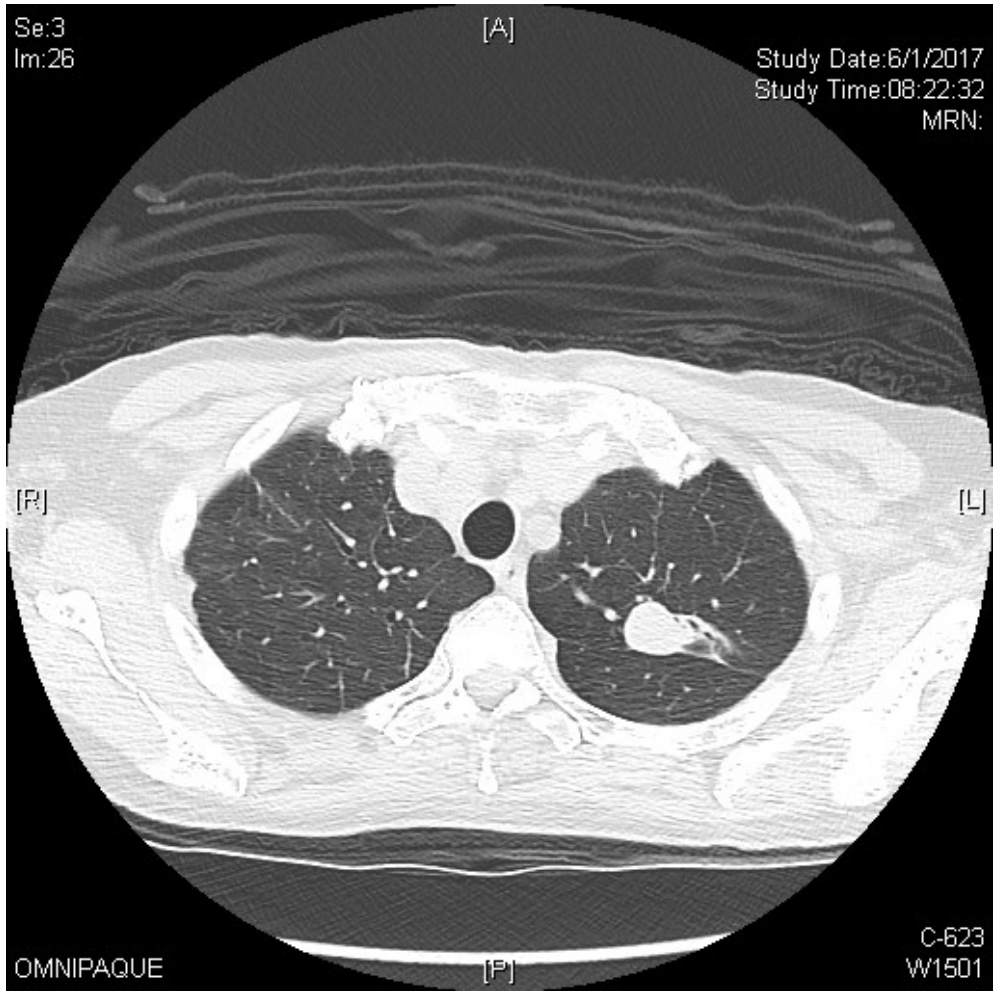
- Accounts for 10-15% of lung tumors.
- >30 K patients diagnosed every year in the US.
- Most patients present with metastatic disease.
- Survival of untreated disease with weeks-months.
- Most patients respond well to chemotherapy initially
- With treatment median OS 8-13 months. With <5% of patients alive within 2 years.

Staging

- For treatment purposes its divided between limited and extensive stage. Depending on the radiation field.
- TNM follows that of NSCLC.

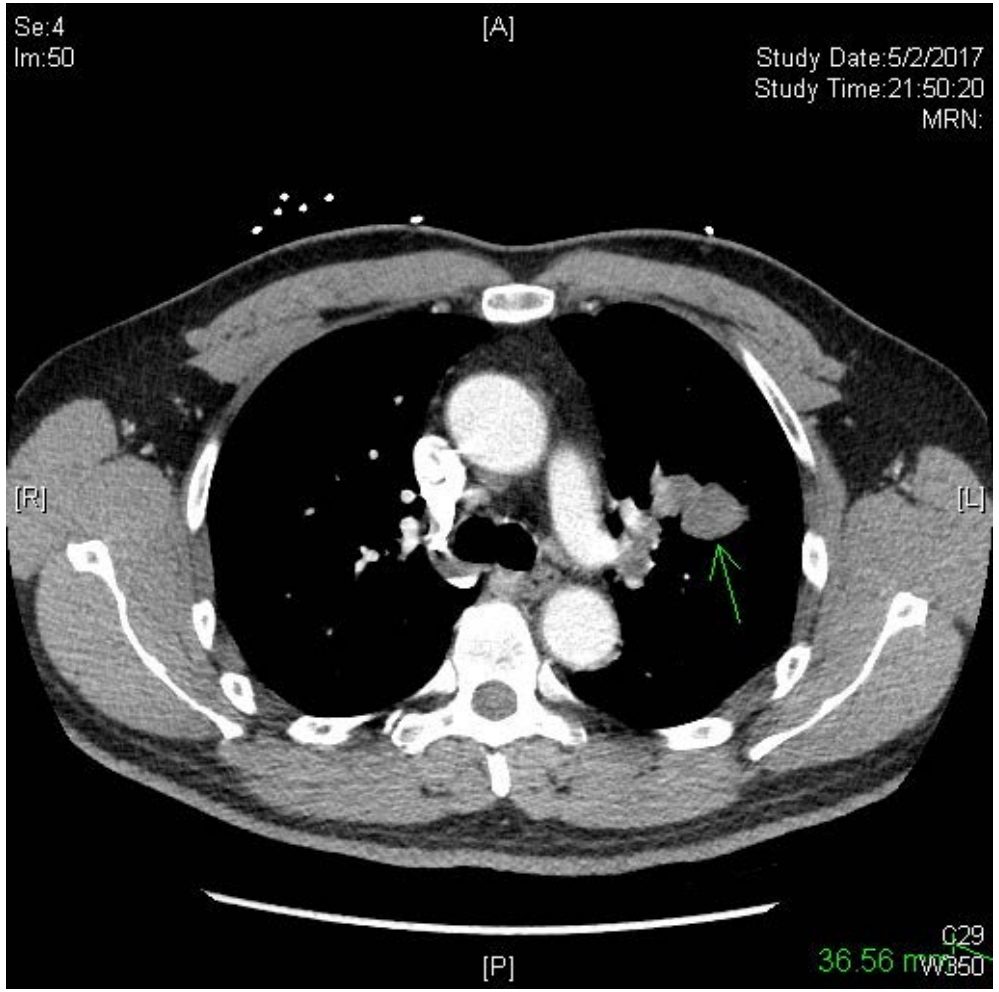
Stage 1

- 78 yo M, no symptoms. Incidental nodule found for unrelated reasons.
- PET no evidence of disease elsewhere.
- Taken to surgery.
- Histology reveals SCLC
- Now what?
- Adjuvant platinum based treatment.



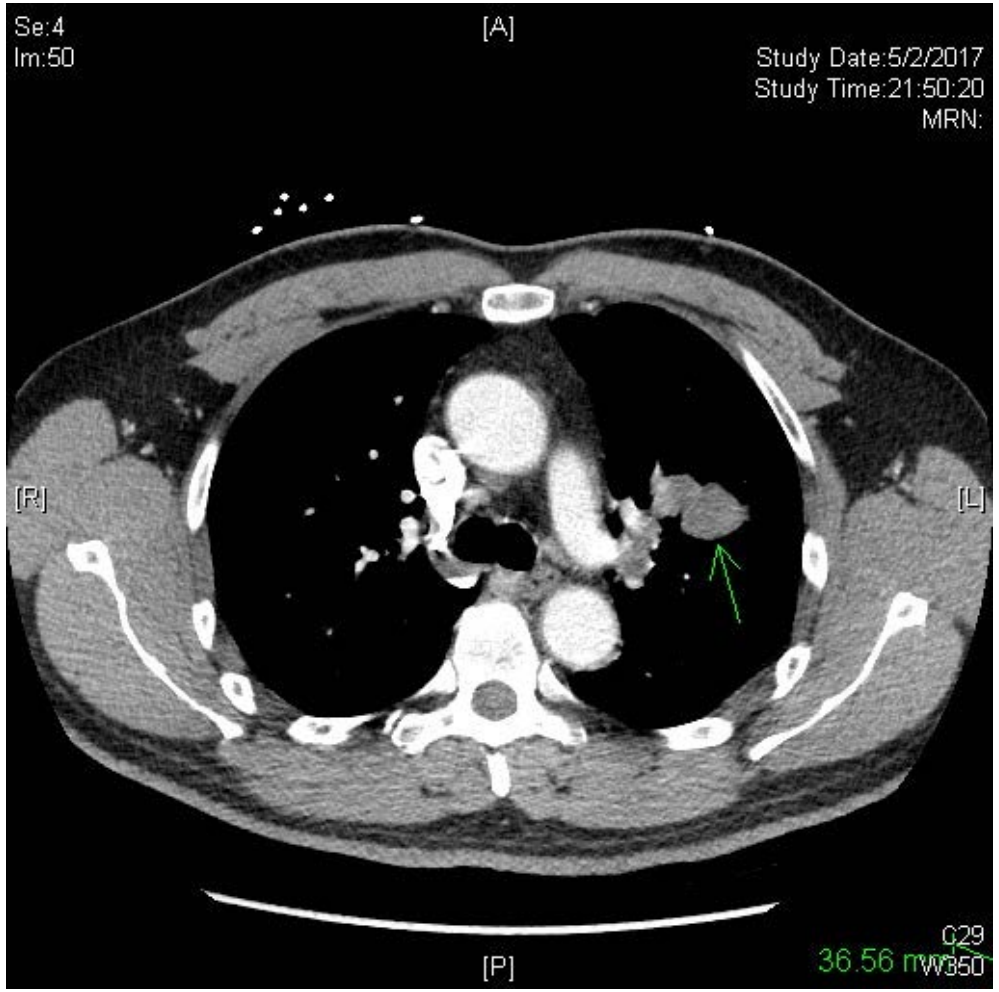
Limited stage

- 58 yo M presents with hemoptysis. Imaging reveals a midlung mass.
- Biopsy shows SCLC

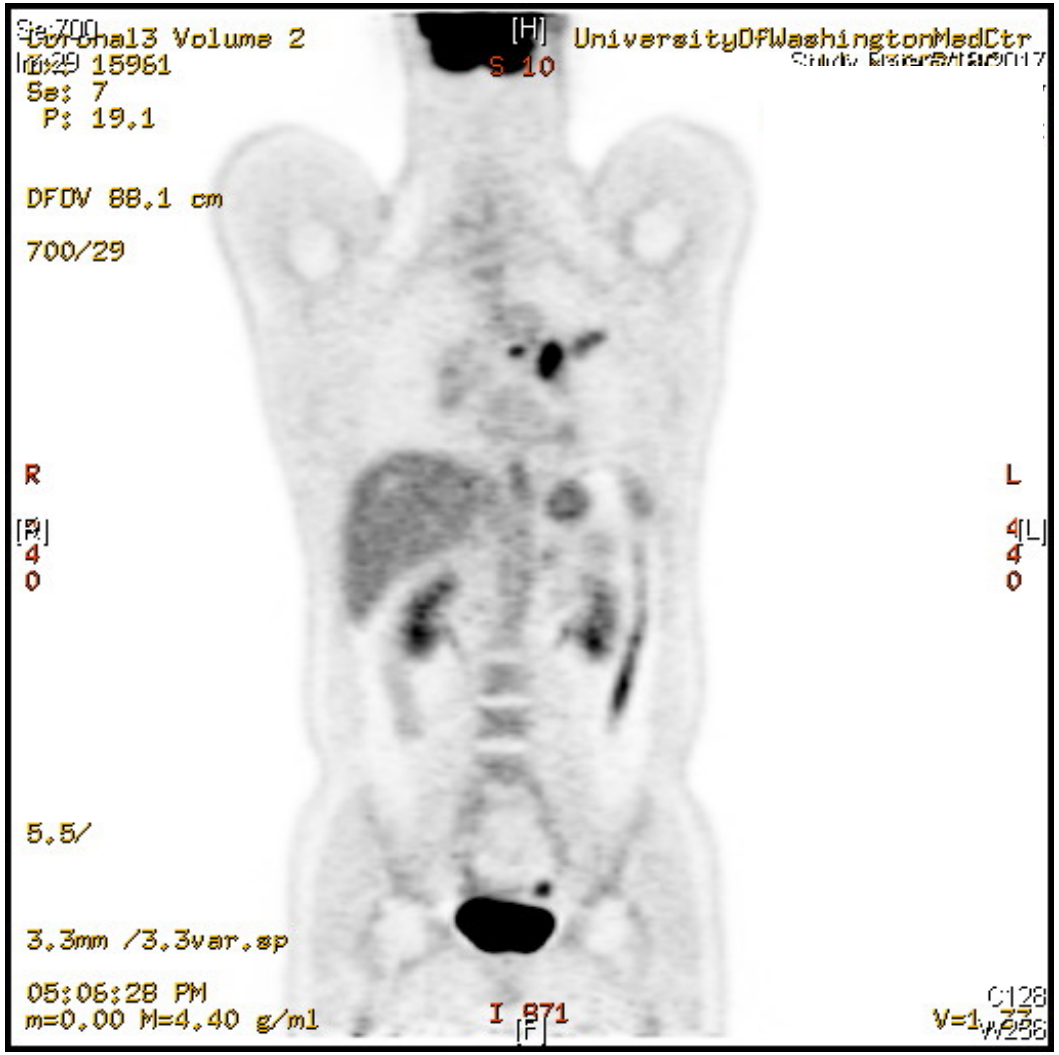


Workup should include

- CT scan: Chest and abdomen
- PET scan/Bone scan.
- If there is no evidence of distant metastatic disease.
- MRI brain.
- Bone marrow if unexplained hematologic abnormality is present.



PET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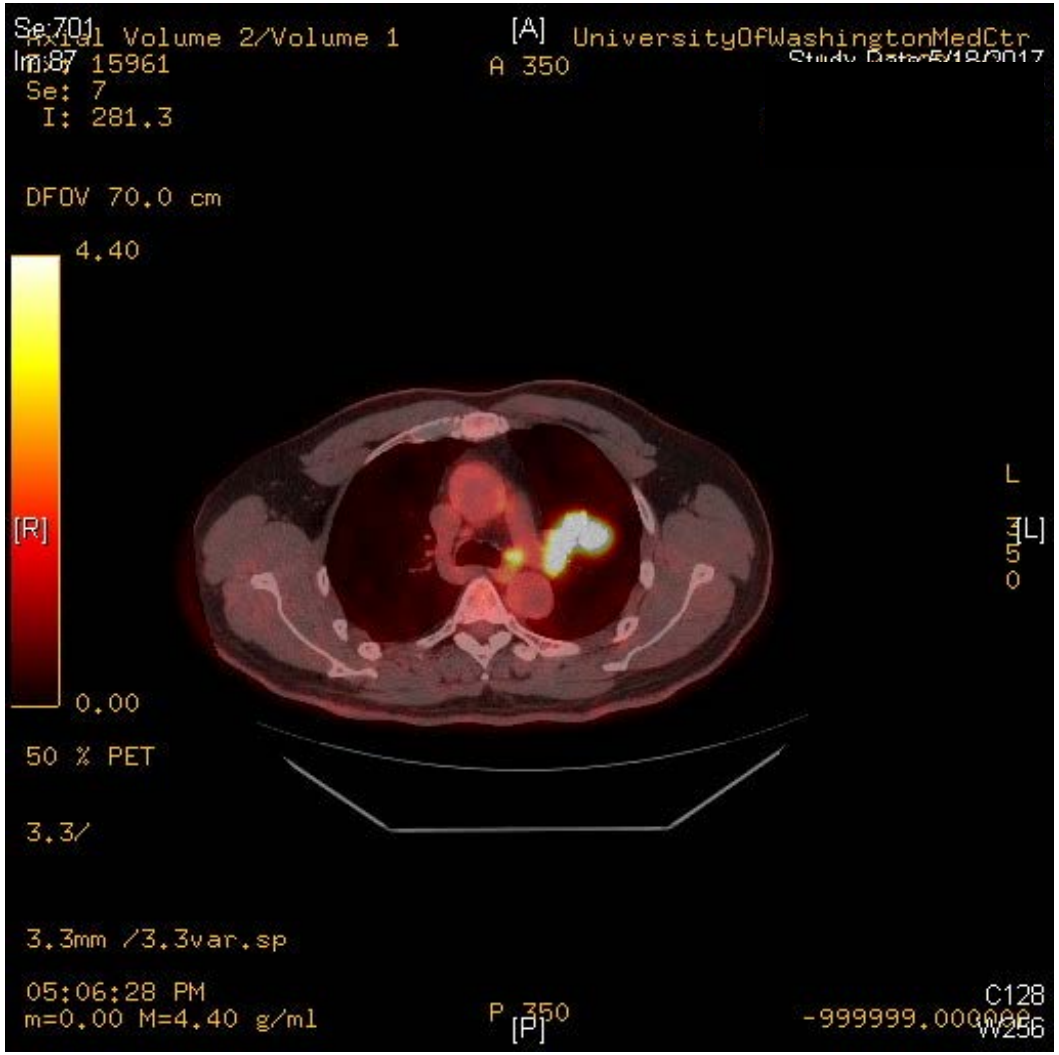
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W256

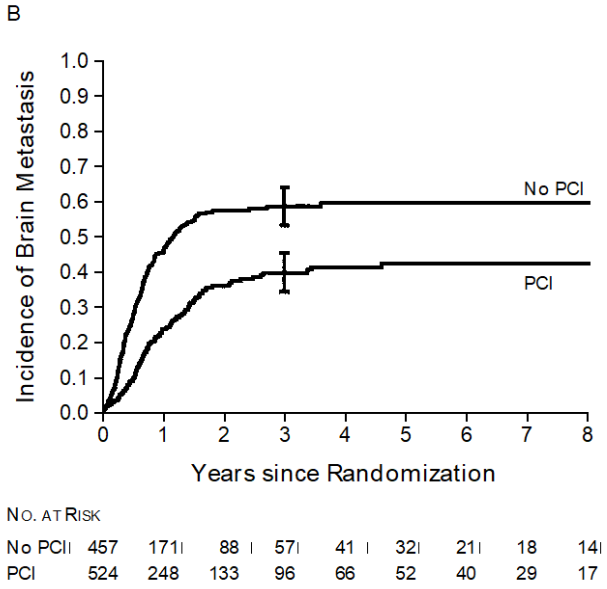
Treatment

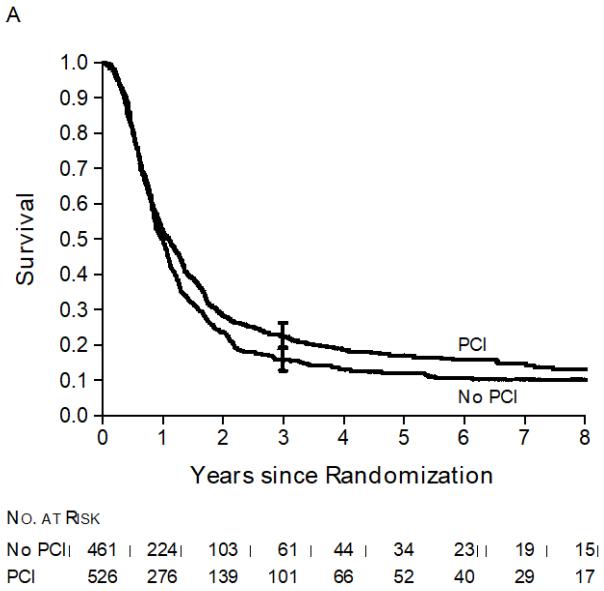
- Main stay of treatment should be chemotherapy and radiation.
- Cisplatin and Etoposide is SOC.
- Cis day 1. Etop Days1-3 q 21 days
- Carboplatin can be considered. Although controversial.
- Radiation can start during second cycle.
- Once vs twice daily radiation is currently controversial.

Rossi, et. al Carboplatin- or cisplatin-based chemotherapy in first-line treatment of small-cell lung cancer: the COCIS meta-analysis of individual patient data. JCO. 2012. PMID. 22473169

After Chemoradiation

- PCI. Associated with a clear survival benefit. RR 0.84; 95% CI 0.73-0.97, which corresponded to an increase in the three-year survival rate from 15.3 to 20.7





Auperin, N Engl J Med. 1999. PMID 10441603

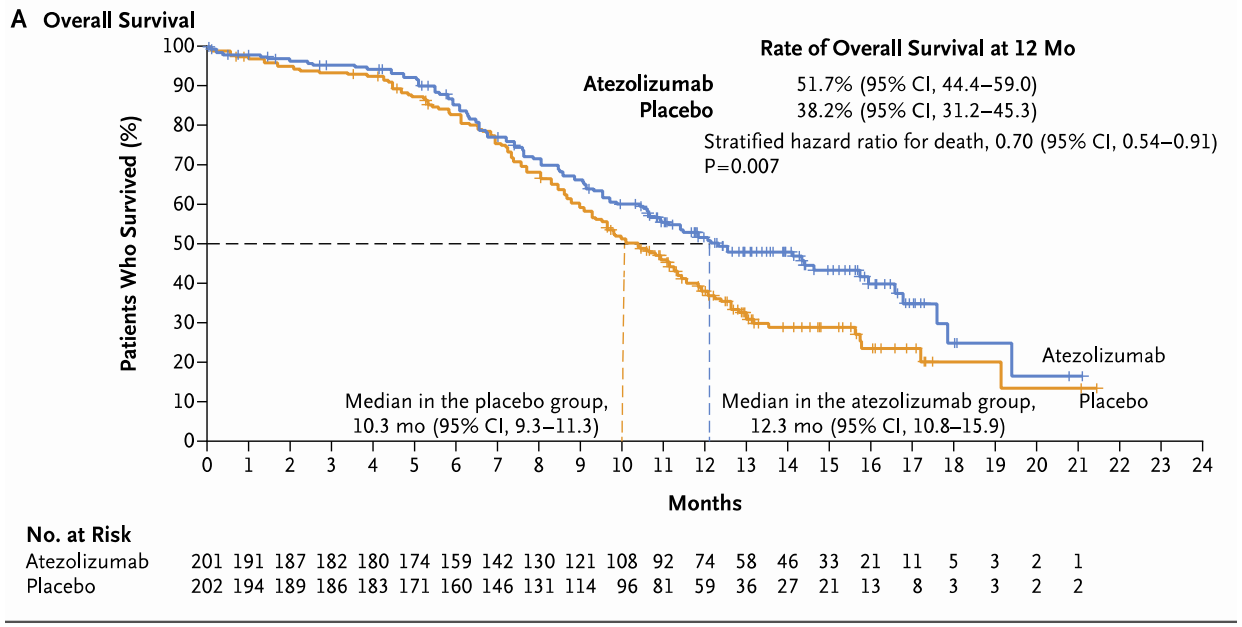
Extensive Stage.

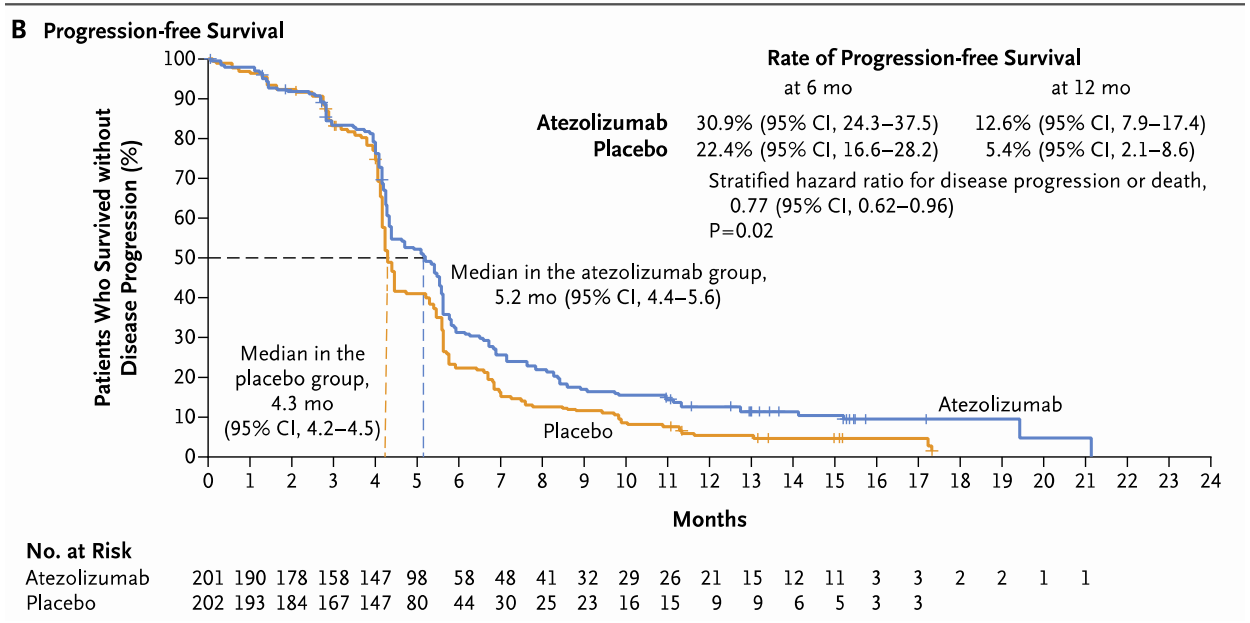
- Rapidly growing disease.
- Post obstructive pneumonia.
- SVC Syndrome.
- Para neoplastic phenomena
  - Hyponatremia
  - Eaton-Lambert
  - ACTH secretion
- Bone marrow infiltration.

Treatment for extensive stage.

- Main treatment challenge is decide when to start treatment.
- Are symptoms due to disease vs poor overall health.
  - Poor PS.
  - Liver failure.
  - BM infiltrations
- New current standard of care is chemotherapy and immunotherapy concurrently.

Chemoimmunotherapy





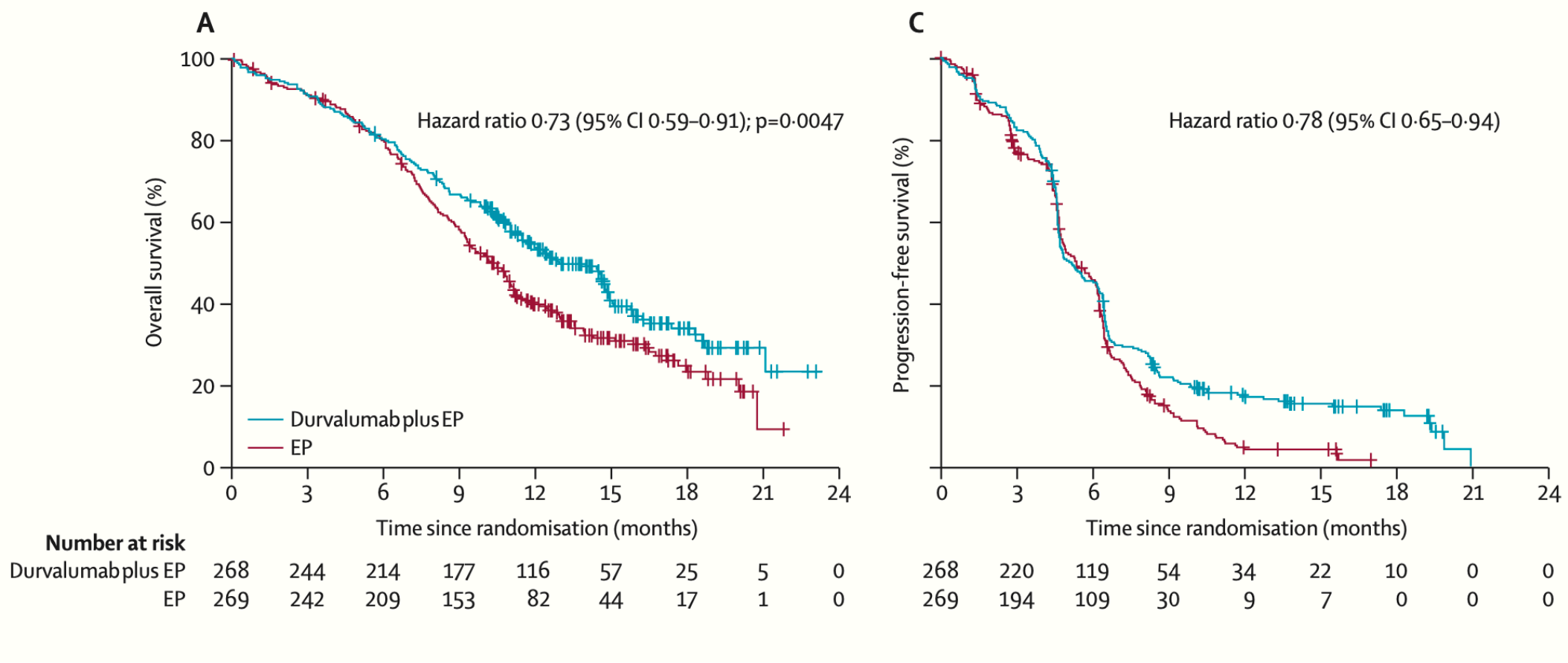
Horn, NEJM 2018

- No increase in AE in patients treated with atezo.

Table 3. Adverse Events Related to the Trial Regimen.*

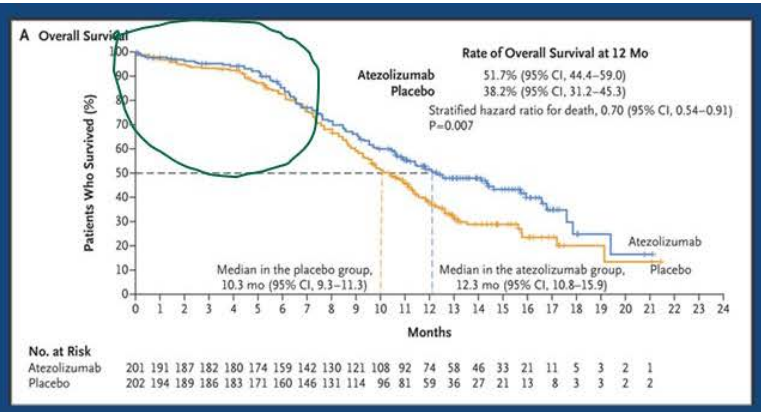
Event	Atezolizumab Group (N = 198)			Placebo Group (N = 196)		
	Grade 1 or 2	Grade 3 or 4	Grade 5	Grade 1 or 2	Grade 3 or 4	Grade 5
	number of patients (percent)					
Any adverse event	73 (36.9)	112 (56.6)	3 (1.5)	68 (34.7)	110 (56.1)	3 (1.5)
Adverse events with an incidence of ≥10% in any grade category or events of grade 3 or 4 with an incidence of ≥2% in either group						
Neutropenia	26 (13.1)	45 (22.7)	1 (0.5)	20 (10.2)	48 (24.5)	0
Anemia	49 (24.7)	28 (14.1)	0	41 (20.9)	24 (12.2)	0
Alopecia	69 (34.8)	0	0	66 (33.7)	0	0
Nausea	62 (31.3)	1 (0.5)	0	58 (29.6)	1 (0.5)	0
Fatigue	39 (19.7)	3 (1.5)	0	37 (18.9)	1 (0.5)	0
Decreased neutrophil count	7 (3.5)	28 (14.1)	0	12 (6.1)	33 (16.8)	0
Decreased appetite	39 (19.7)	2 (1.0)	0	26 (13.3)	0	0
Thrombocytopenia	12 (6.1)	20 (10.1)	0	14 (7.1)	15 (7.7)	0
Decreased platelet count	17 (8.6)	7 (3.5)	0	21 (10.7)	7 (3.6)	0
Vomiting	25 (12.6)	2 (1.0)	0	19 (9.7)	3 (1.5)	0
Constipation	19 (9.6)	1 (0.5)	0	25 (12.8)	0	0
Leukopenia	15 (7.6)	10 (5.1)	0	10 (5.1)	8 (4.1)	0
Decreased white-cell count	10 (5.1)	6 (3.0)	0	16 (8.2)	9 (4.6)	0
Diarrhea	15 (7.6)	4 (2.0)	0	18 (9.2)	1 (0.5)	0
Febrile neutropenia	0	6 (3.0)	0	0	12 (6.1)	0
Infusion-related reaction	6 (3.0)	4 (2.0)	0	9 (4.6)	1 (0.5)	0

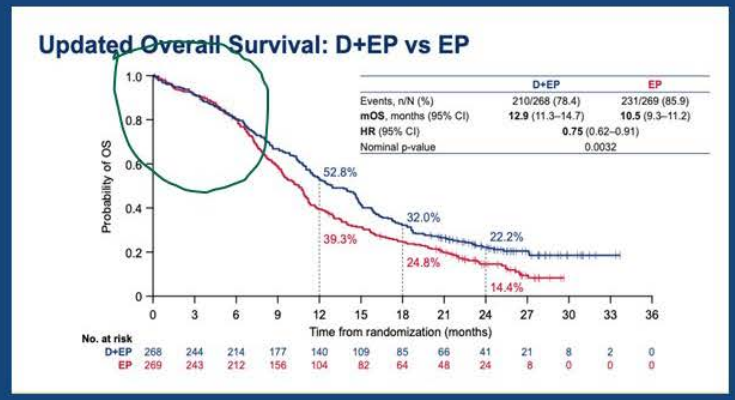
Results confirmed with durvalumab

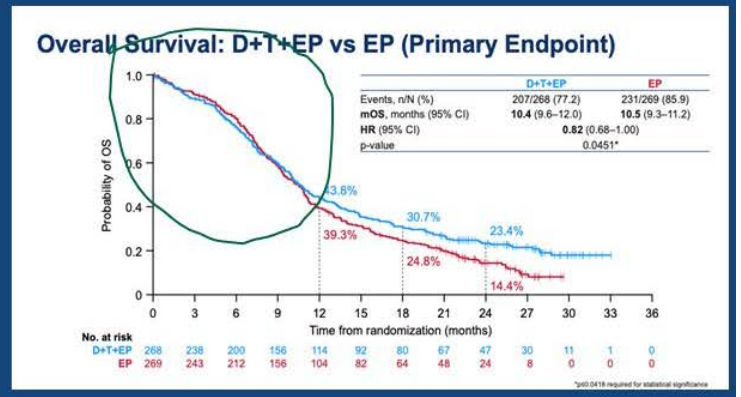


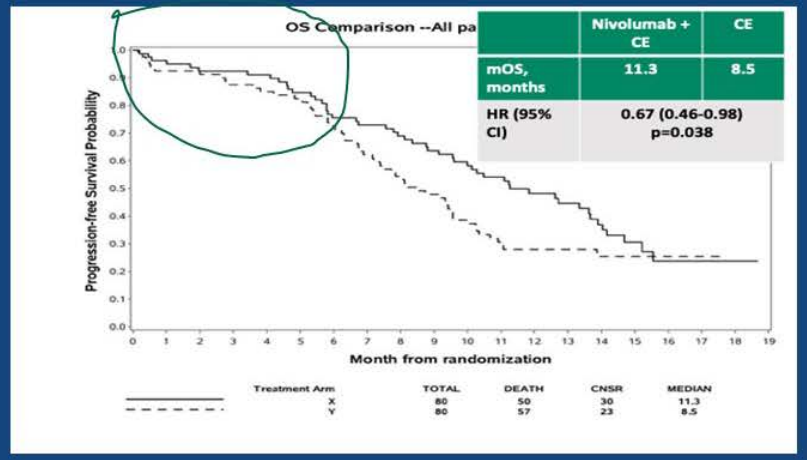
Paz-Ares, Lancet 2019

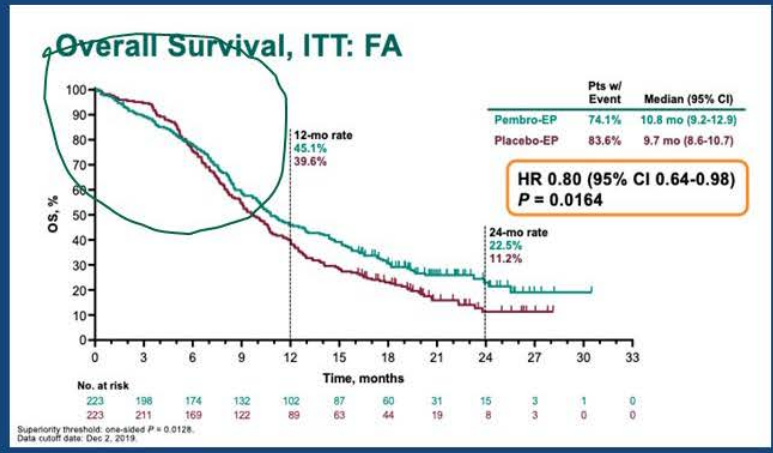
And Nivo and Pembro











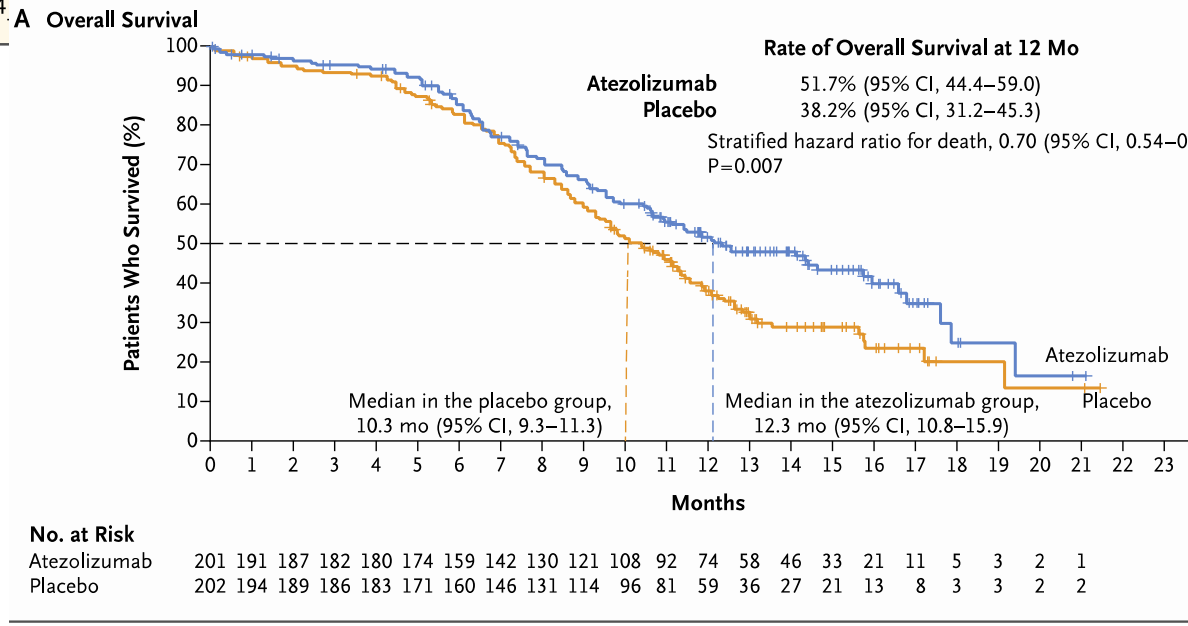
Chemoimmunotherapy

Table 2. Response Rate, Duration of Response, and Disease Progression.*

Variable	Atezolizumab Group (N = 201)	Placebo Group (N = 202)
Objective confirmed response†	121 (60.2 [53.1–67.0])	130 (64.4 [57.3–71.0])
Complete response — no. (% [95% CI])	5 (2.5 [0.8–5.7])	2 (1.0 [0.1–3.5])
Partial response — no. (% [95% CI])	116 (57.7 [50.6–64.6])	128 (63.4 [56.3–70.0])
Median duration of response (range) — mo‡	4.2 (1.4§–19.5)	3.9 (2.0–16.1§)
Ongoing response at data cutoff — no./total no. (%)	18/121 (14.9)	7/130 (5.4)
Stable disease — no. (% [95% CI])	42 (20.9 [15.5–27.2])	43 (21.3 [15.9–27.6])
Progressive disease — no. (% [95% CI])	22 (10.9 [7.0–16.1])	14 (6.9 [3.8–11.4]

Concerns:

- No “tail” at the end of the curve (although early data)
- No increase in response rate (although 60% RR is tough to beat)
- Unlike NSCLC curves don’t begin to separate until after the chemotherapy period



Horn, NEJM 2018

Chemoimmunotherapy

- Is the new current standard with the addition of atezolizumab or durvalumab to platinum based therapy.
- Carboplatin is associated with less toxicities in the metastatic setting, no decrease in efficacy compared to carboplatin.
- In real life most patients receive a dose of chemotherapy alone before adding immunotherapy

Slotman Study

- Patients needed to have “responsive therapy”.
- ECOG 0-2.
- No evidence of brain metastasis.
- No MRI required.
- 286 patients
- No follow-up imaging

Slotman, B. N Engl J Med. 2007

Table 2. Scores on Quality-of-Life Assessment.*

Quality-of-Life Score	Assessment Time	Prophylactic Cranial Irradiation	Control	P Value†
Primary end points				
Global health status	0–9 mo‡			0.10
Role functioning	0–9 mo‡			0.17
Cognitive functioning	0–9 mo‡			0.07
Emotional functioning	0–9 mo‡			0.18
Fatigue	6 wk	43.2±2.56	29.3±2.47	<0.001
	3 mo	53.6±3.03	38.5±3.24	<0.001
Hair loss	6 wk	36.5±3.96	11.7±3.73	<0.001
Exploratory results				
Appetite loss	6 wk	28.9±3.25	10.6±3.06	<0.001
	3 mo	43.9±3.87	14.8±4.18	<0.001
Nausea and vomiting	6 wk	15.0±1.73	5.3±1.64	<0.001
	3 mo	26.9±2.92	8.2±3.15	<0.001
Leg weakness	6 wk	25.2±2.71	11.8±2.48	<0.001
	3 mo	32.2±3.62	16.0±3.93	0.003

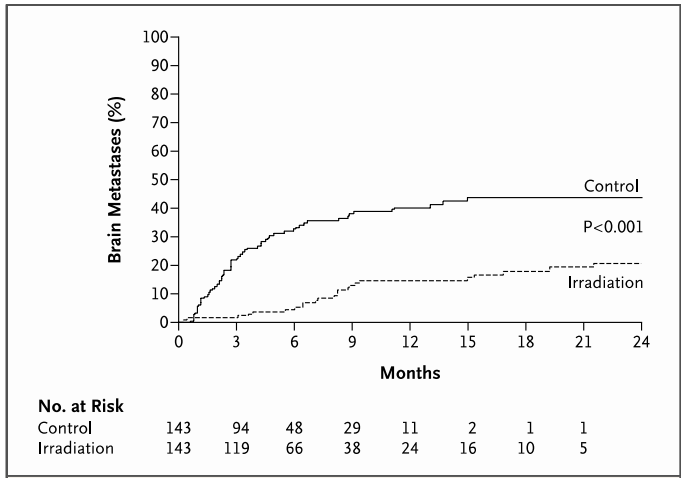


Figure 1. Cumulative Incidence of Symptomatic Brain Metastases.
The difference in the cumulative incidence of brain metastases between the irradiation group and the control group was significant (P<0.001, by Gray's method).

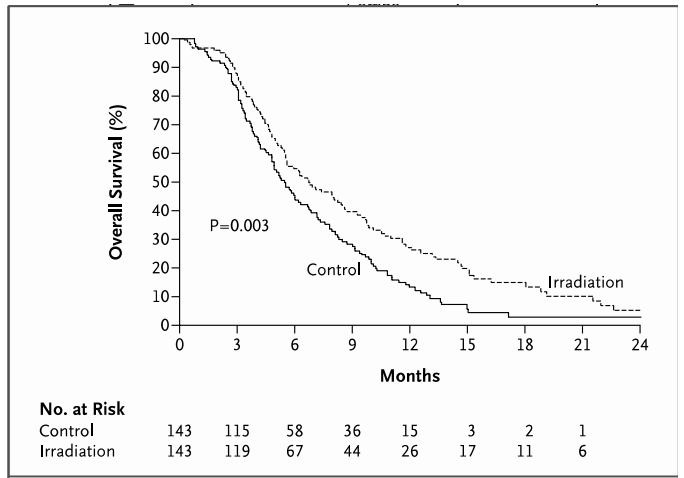
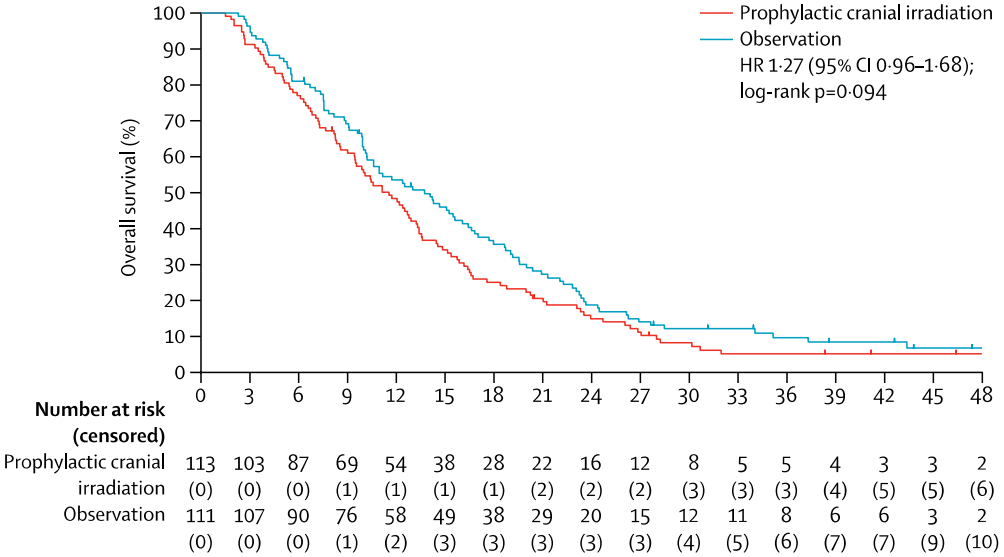
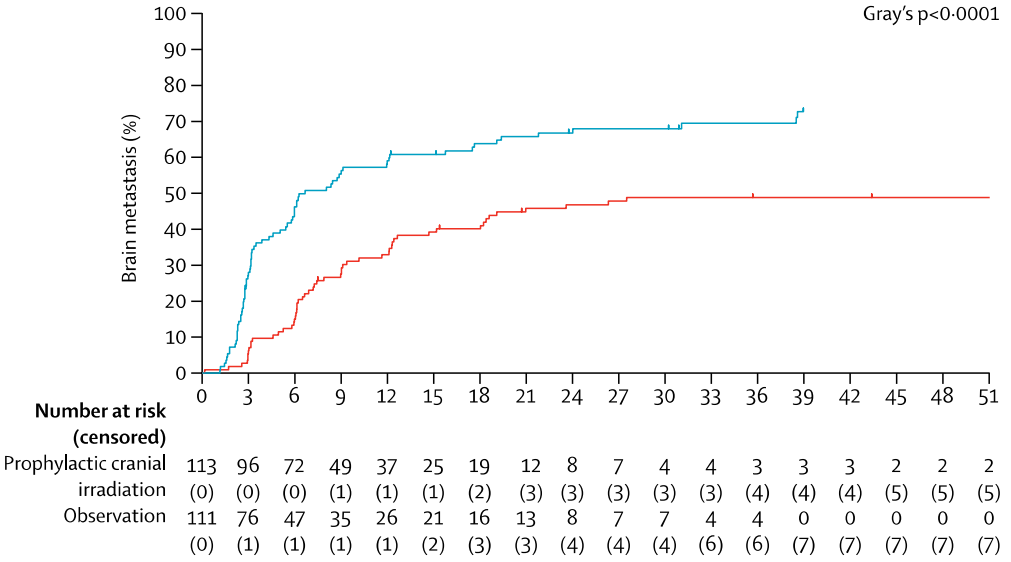


Figure 3. Overall Survival.
Patients in the irradiation group had a longer median overall survival (6.7 months) than did those in the control group (5.4 months) (P=0.003; hazard ratio, 0.68; 95% CI, 0.52 to 0.88).

Takahashi study

- Patients needed to have “responsive therapy”.
- ECOG 0-2.
- No evidence of brain metastasis with a screening MRI.
- Follow up MRI q 3 months <u>required</u>.





Takahashi et. al. Lancet Oncol. 2017. PMID 28343976

Thoracic radiation.

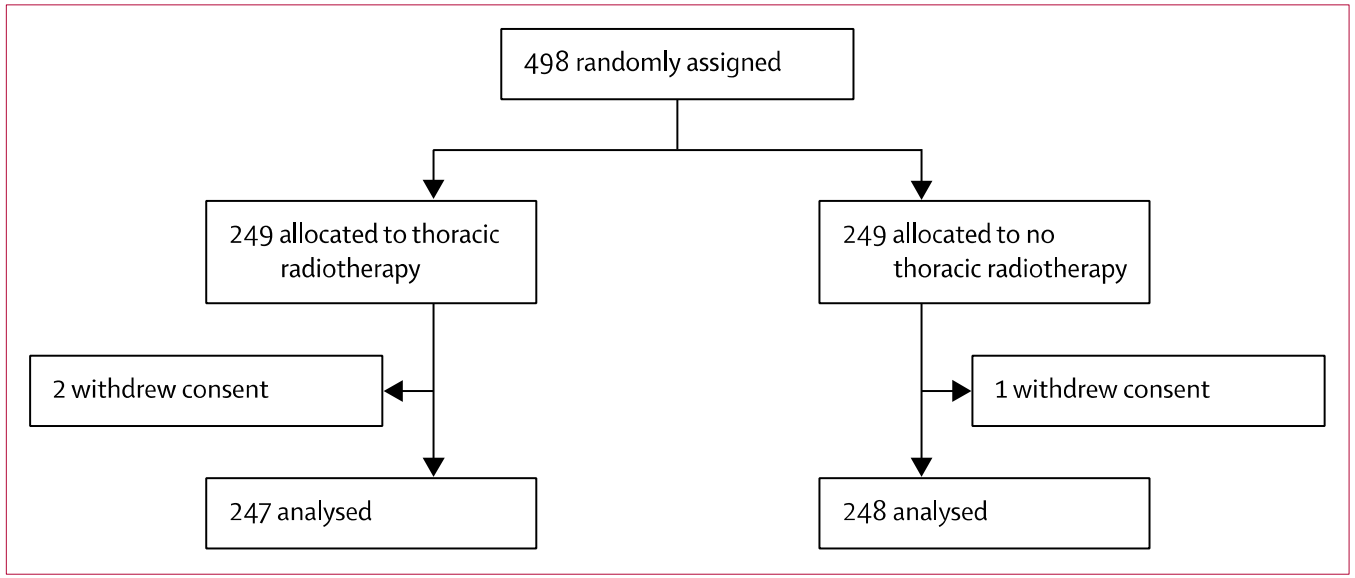
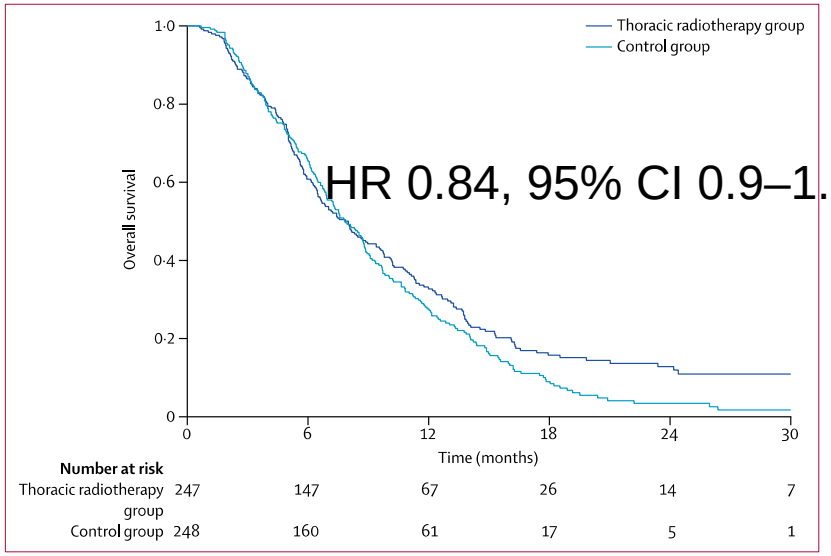


Figure 1: **Trial profile**



HR 0.84, 95% CI 0.9–1.01, p=0·066

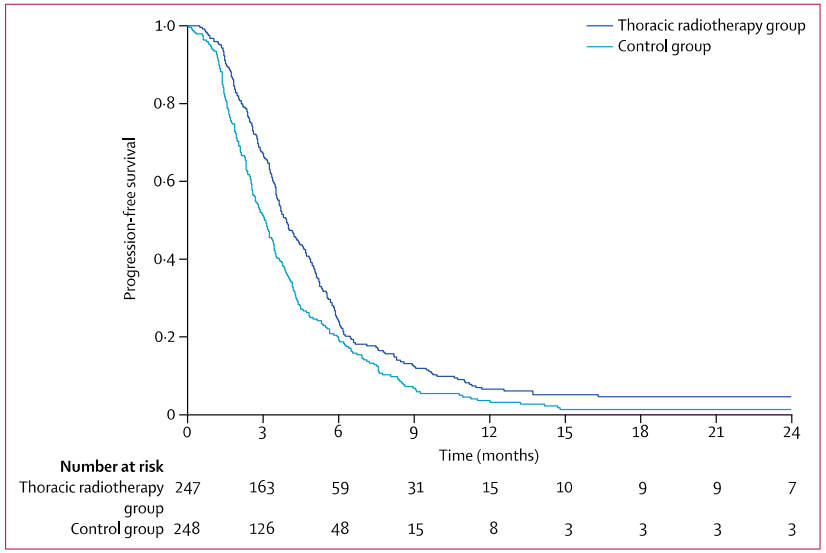


Figure 4: **Kaplan-Meier curves for progression-free survival**

Slotman et. al. Lancet Oncol. 2015.

Thoracic and extratoracic radiation

- RTOG 0937. Phase 2 study. PCI vs PCI vs ”consolidative” xrt up to 4 metastatic lesions.
- Interim analysis showed no difference in 1 year survival rate (60.1 PCI alone vs 50.8 in PCI + XRT (p=0.21) and the study was stopped for futility.
- With the current standard of chemoimmunotherapy and maintenance immunotherapy there is no data as to what to do with the PD1/PDL1 agent.

What to do at relapse? Second line chemotherapy

Phase III Trial Comparing Supportive Care Alone With Supportive Care With Oral Topotecan in Patients With Relapsed Small-Cell Lung Cancer

Mary E.R. O'Brien, Tudor-Eliade Ciuleanu, Hristo Tsekov, Yaroslav Shparyk, Branka Čučeviá, Gabor Juhasz, Nicholas Thatcher, Graham A. Ross, Graham C. Dane, and Theresa Crofts

A B S T R A C T

Purpose
For patients with small-cell lung cancer (SCLC), further chemotherapy is routinely considered at relapse after first-line therapy. However, proof of clinical benefit has not been documented.

Patients and Methods
This study randomly assigned patients with relapsed SCLC not considered as candidates for standard intravenous therapy to best supportive care (BSC) alone (n = 70) or oral topotecan (2.3 mg/m^2/d, days 1 through 5, every 21 days) plus BSC (topotecan; n = 71).

Results
In the intent-to-treat population, survival (primary end point) was prolonged in the topotecan group (log-rank P = .0104). Median survival with BSC was 13.9 weeks (95% CI, 11.1 to 18.6) and with topotecan, 25.9 weeks (95% CI, 18.3 to 31.6). Statistical significance for survival was maintained in a subgroup of patients with a short treatment-free interval (≤ 60 days). Response to topotecan was 7% partial and 44% stable disease. Patients on topotecan had slower quality of life deterioration and greater symptom control. Principal toxicities with topotecan were hematological: grade 4 neutropenia, 33%; grade 4 thrombocytopenia, 7%; and grade 3/4 anemia, 25%. Comparing topotecan with BSC, infection ≥ grade 2 was 14% versus 12% and sepsis 4% versus 1%; other grade 3/4 events included vomiting 3% versus 0, diarrhea 6% versus 0, dyspnea 3% versus 9%, and pain 3% versus 6%. Toxic deaths occurred in four patients (6%) in the topotecan arm. All cause mortality within 30 days of random assignment was 13% on BSC and 7% on topotecan.

Conclusion
Chemotherapy with oral topotecan is associated with prolongation of survival and quality of life benefit in patients with relapsed SCLC.

J Clin Oncol 24:5441-5447. © 2006 by American Society of Clinical Oncology

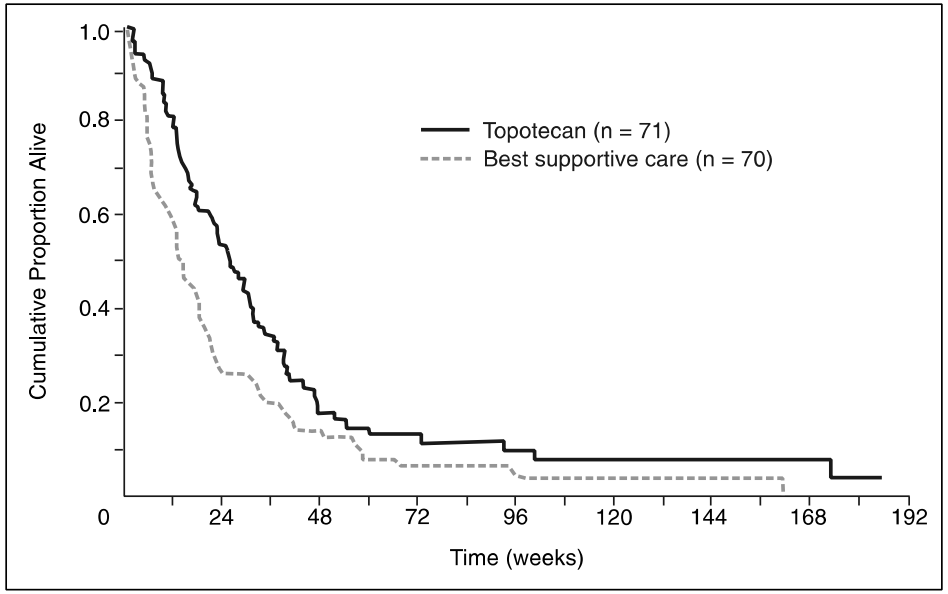


Fig 1. Kaplan-Meier estimates for overall survival in the intent-to-treat population (log-rank P = .01). The unadjusted hazard ratio for overall survival was 0.64 (95% CI, 0.45 to 0.90) for topotecan relative to best supportive care alone. Adjusted for stratification factors, the hazard ratio was 0.61 (95% CI, 0.43 to 0.87).

Lurbinectedin

- Is a selective inhibitor of transcription that binds preferentially to guanines located in the GC-rich regulatory areas of DNA gene promoters.
- Found to have activity on early Phase 1 studies.
- Phase 3 in combination with doxorubicin versus topotecan or CAV has finished accrual.
- Phase 2 confirmed activity as a single agent.

Lurbinectedin

- 105 patients enrolled.
- No active CNS metastasis.
- 45 had <90 days chemotherapy free interval and 60 had more.
- Most except 7 patients were treated after only 1 line of therapy.
- ORR. 35% (n=35).
- PFS 3.5 months
- OS 9.3 months.
- This led to its FDA approval.

Second line chemotherapy

- Other second line agents are also effective.
  - Paclitaxel.[1]
  - Gemcitabine.[2]
  - Irinotecan.[3]
- Response rates single digits
- Immunotherapy should not be given if first line contained a PD1/PDL1 agent.

1. Smit. Br J Cancer. 1998. PMID. 9461009
2. Masters. J Clin Oncol. 2003. PMID. 12697880
3. Masuda. J Clin Oncol. 1992. PMID. 1321891


Questions