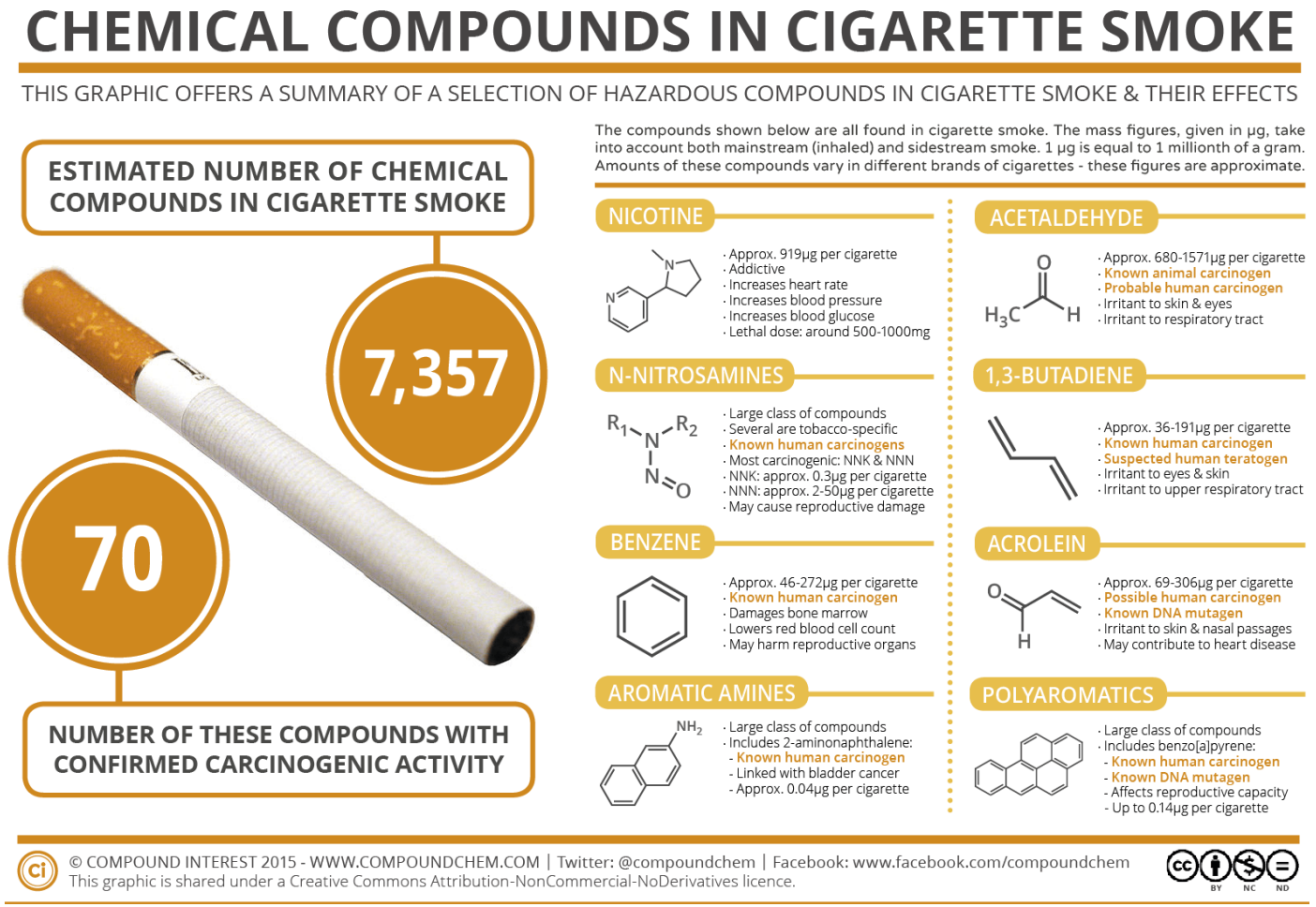
Small Cell Lung Cancer

Evolving Treatments for the Oncology Practice

Erin Schenk M.D., Ph.D.
Assistant Professor of Medicine
Division of Medical Oncology
Anschutz Medical Campus
University of Colorado

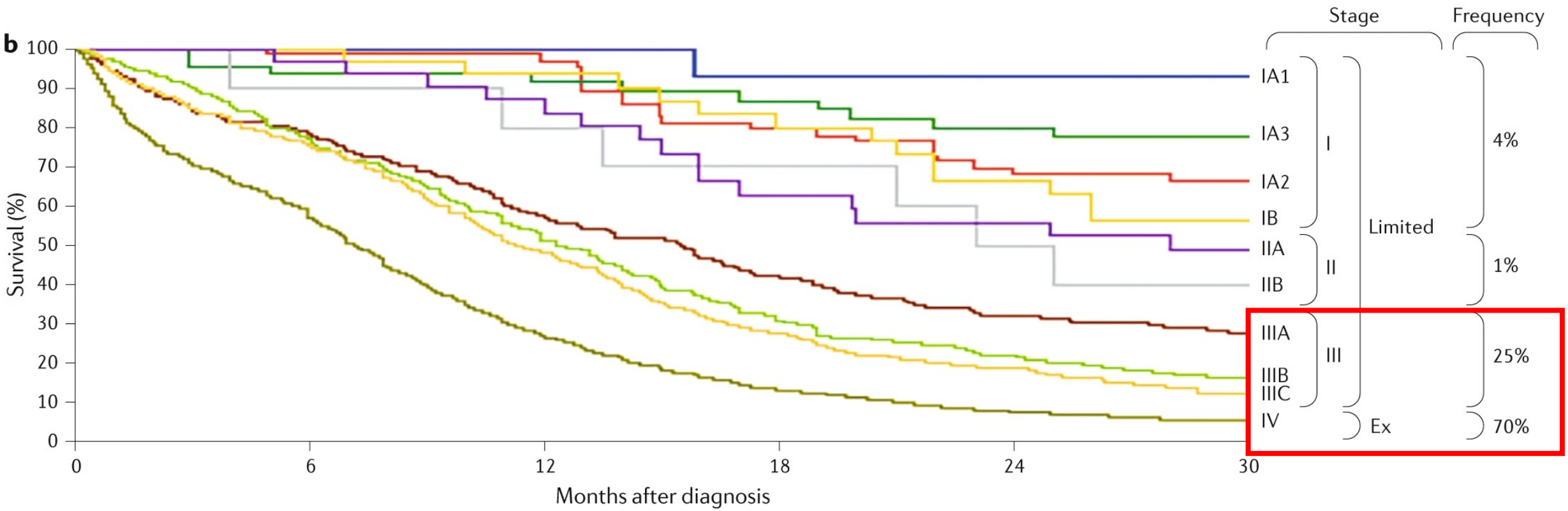
Epidemiology of SCLC

- Smoking associated
  - Pack years
    - 1st 50 PY confers most risk
  - Age of initiation
  - Duration of smoking
  - Cigarettes/day
- Never smokers
  - 2% of SCLC patients
  - Role for radon, air pollution
  - NSCLC transformation



Huang R *et al.* eBioscience Volume 2, Issue 11, November 2015, Pages 1677-1685

SCLC Staging Distribution and Survival



Rudin CM et al. Nature Reviews Disease Primers volume 7, Article number: 3 (2021)

Systemic Therapy for SCLC
EP as SOC for Decades

Limited Stage SCLC

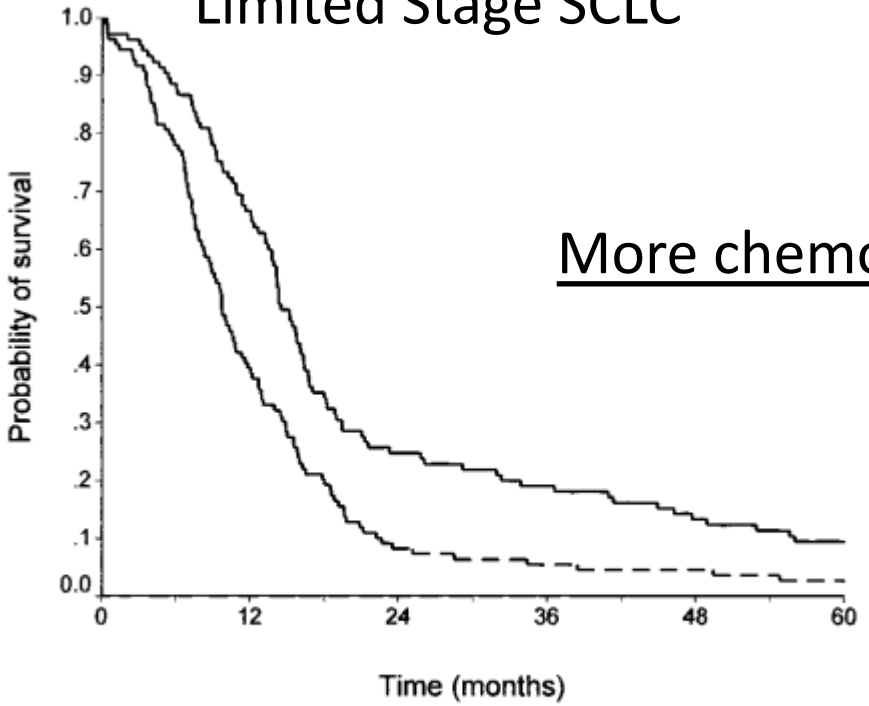


Fig 2. Overall survival of LD-SCLC patients (N = 214) according to treatment arm (P = .0001). CEV (dashed line), n = 109; EP (solid line), n = 105.

Extensive Stage SCLC

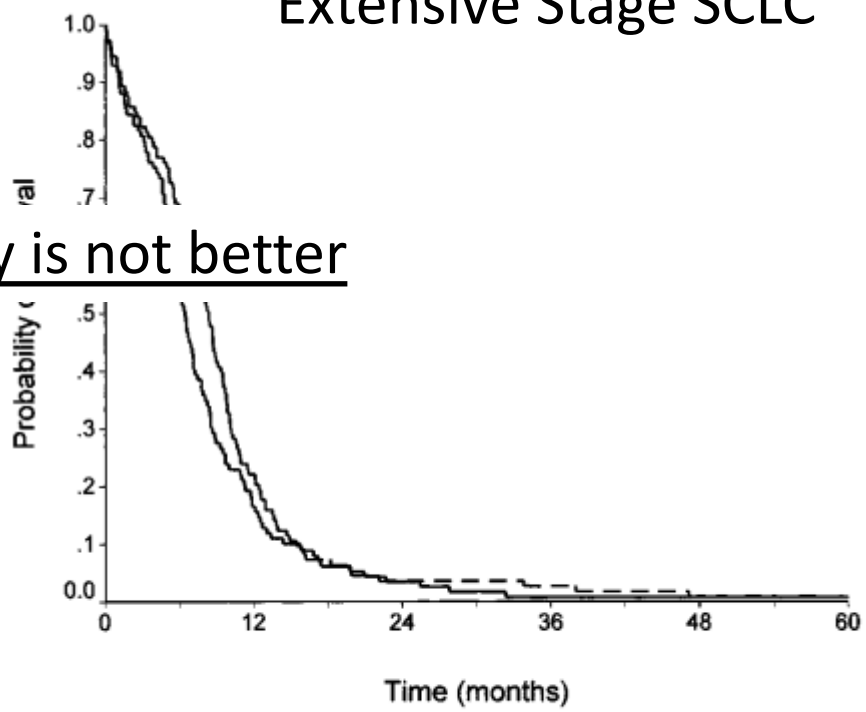


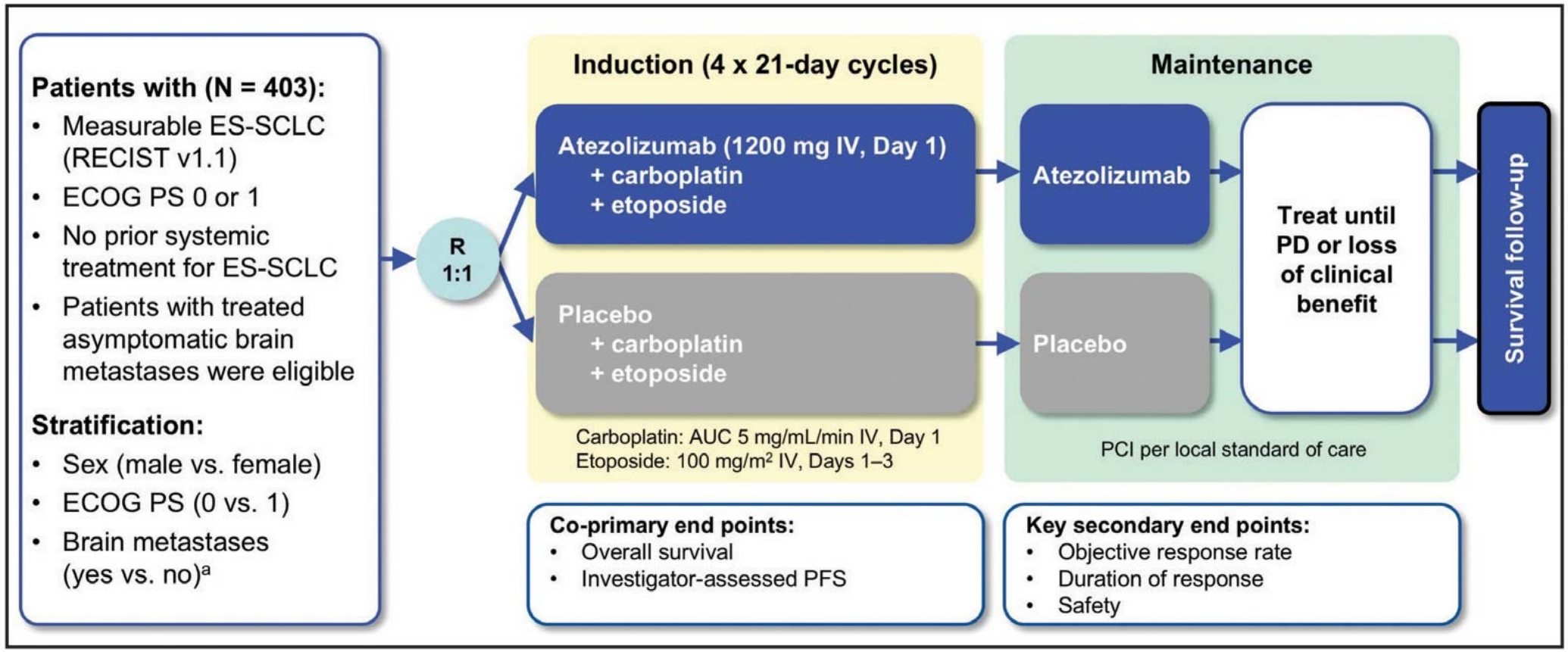
Fig 3. Overall survival of ED-SCLC patients (n = 222) according to treatment arm (P = .21). CEV (dashed line), n = 109; EP (solid line), n = 113.

More chemotherapy is not better

Stein Sundstrøm *et al.* J Clin Oncol. 2002 Dec 15;20(24):4665-72

First Line Therapy for ES-SCLC

IMpower133



Horn L *et al.* N Engl J Med. 2018 Dec 6;379(23):2220-2229

IMpower133

- **OS (primary endpoint)**:

12.3 vs 10.3 mo

HR 0.70 (CI 0.54 – 0.91), p = 0.007

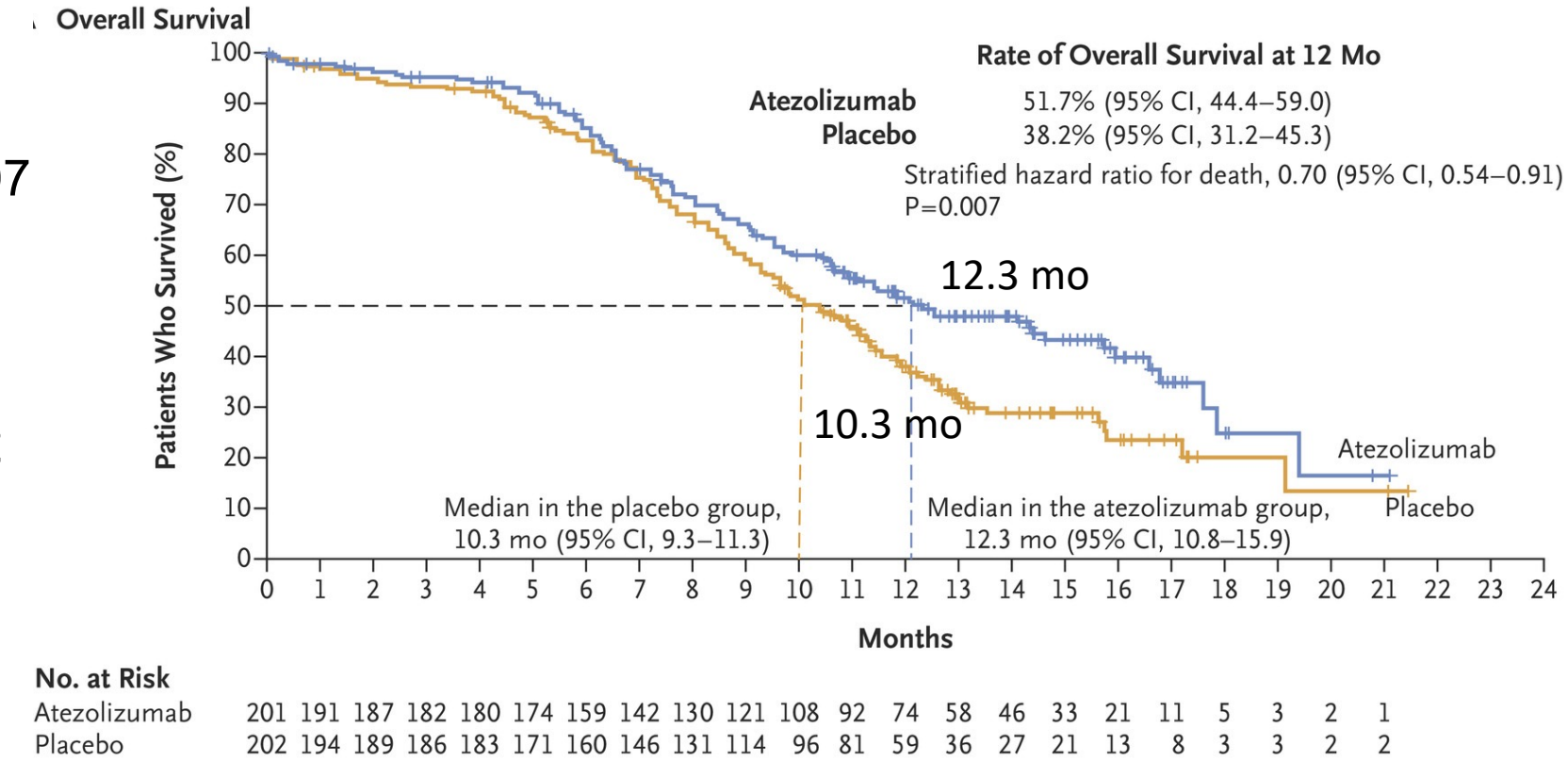
- **PFS (primary endpoint)**:

5.2 vs 4.3 mo

HR 0.52 (CI 0.62 – 0.96), p = 0.02

- **Response rate**:

60.2 vs 64.4%

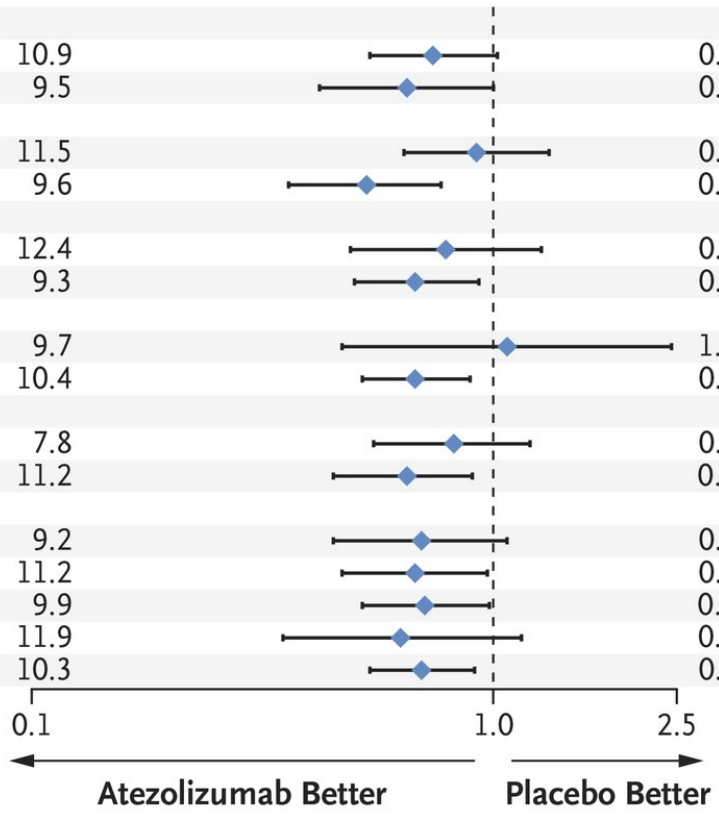


Horn L *et al.* N Engl J Med. 2018 Dec 6;379(23):2220-2229

IMpower133

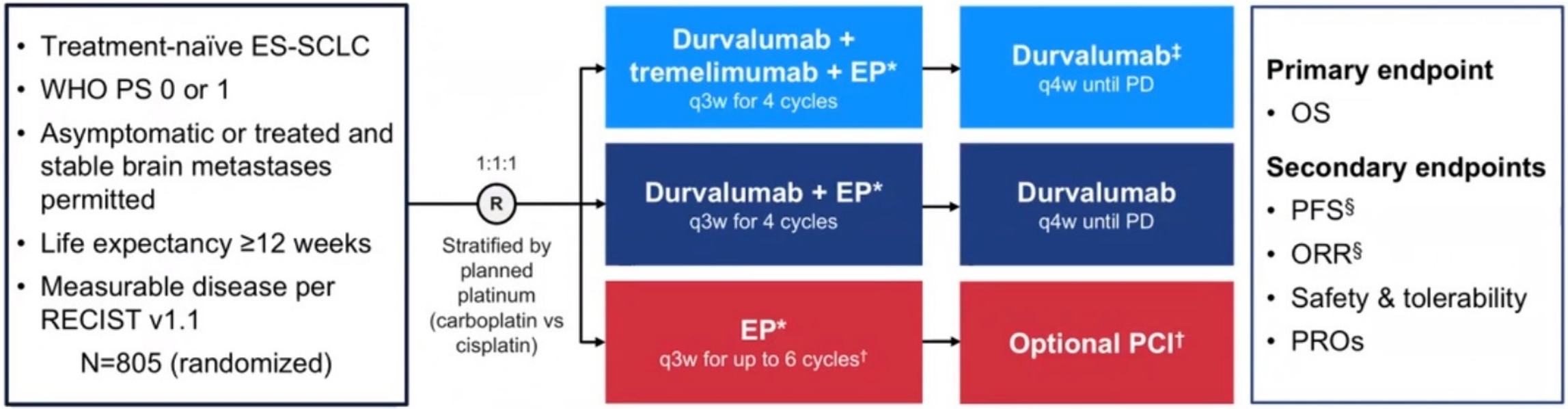
C Overall Survival According to Baseline Characteristics

Subgroup	No. of Patients (%)	Median Overall Survival (mo)		Hazard Ratio for Death (95% CI)
		Atezolizumab	Placebo	
Sex				
Male	261 (65)	12.3	10.9	0.74 (0.54–1.02)
Female	142 (35)	12.5	9.5	0.65 (0.42–1.00)
Age				
<65 yr	217 (54)	12.1	11.5	0.92 (0.64–1.32)
≥65 yr	186 (46)	12.5	9.6	0.53 (0.36–0.77)
ECOG score				
0	140 (35)	16.6	12.4	0.79 (0.49–1.27)
1	263 (65)	11.4	9.3	0.68 (0.50–0.93)
Brain metastases				
Yes	35 (9)	8.5	9.7	1.07 (0.47–2.43)
No	368 (91)	12.6	10.4	0.68 (0.52–0.89)
Liver metastases				
Yes	149 (37)	9.3	7.8	0.81 (0.55–1.20)
No	254 (63)	16.8	11.2	0.64 (0.45–0.90)
Tumor mutational burden				
<10 mutations/Mb	139 (34)	11.8	9.2	0.70 (0.45–1.07)
≥10 mutations/Mb	212 (53)	14.6	11.2	0.68 (0.47–0.97)
<16 mutations/Mb	271 (67)	12.5	9.9	0.71 (0.52–0.98)
≥16 mutations/Mb	80 (20)	17.8	11.9	0.63 (0.35–1.15)
Intention-to-treat population	403 (100)	12.3	10.3	0.70 (0.54–0.91)



Horn L *et al.* N Engl J Med. 2018 Dec 6;379(23):2220-2229

CASPIAN Trial

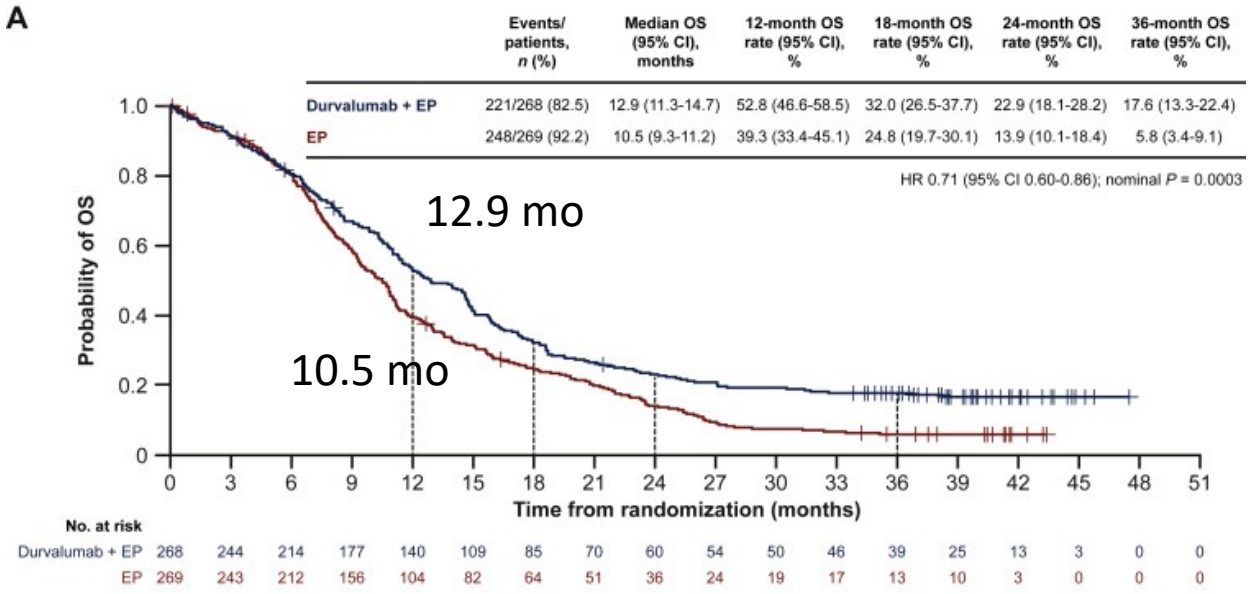


*EP consists of etoposide 80–100 mg/m2 with either carboplatin AUC 5–6 or cisplatin 75–80 mg/m2, durvalumab dosed at 1500 mg, tremelimumab dosed at 75 mg
†Patients could receive an additional 2 cycles of EP (up to 6 cycles total) and PCI at the investigator's discretion
‡Patients received an additional dose of tremelimumab post-EP; §By investigator assessment per RECIST v1.1
AUC, area under the curve; ORR, objective response rate; PCI, prophylactic cranial irradiation; PD, disease progression; PFS, progression-free survival; PROs, patient-reported outcomes; PS, performance status; q3w, every 3 weeks; q4w, every 4 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1

Paz-Ares L et al. Lancet. 2019 Nov 23;394(10212):1929-1939.

CASPIAN Trial

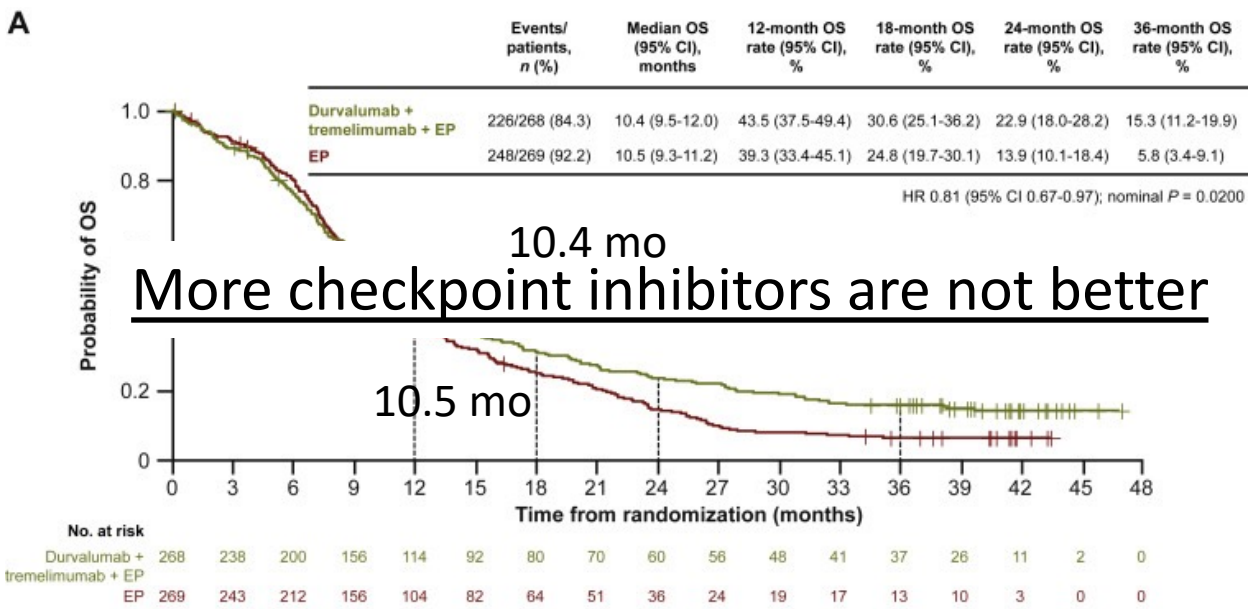
Durvalumab + EP



12.9 v 10.5 mo

HR 0.71 CI 0.60-0.86, p = 0.0003

Durvalumab + Tremelimumab + EP



More checkpoint inhibitors are not better

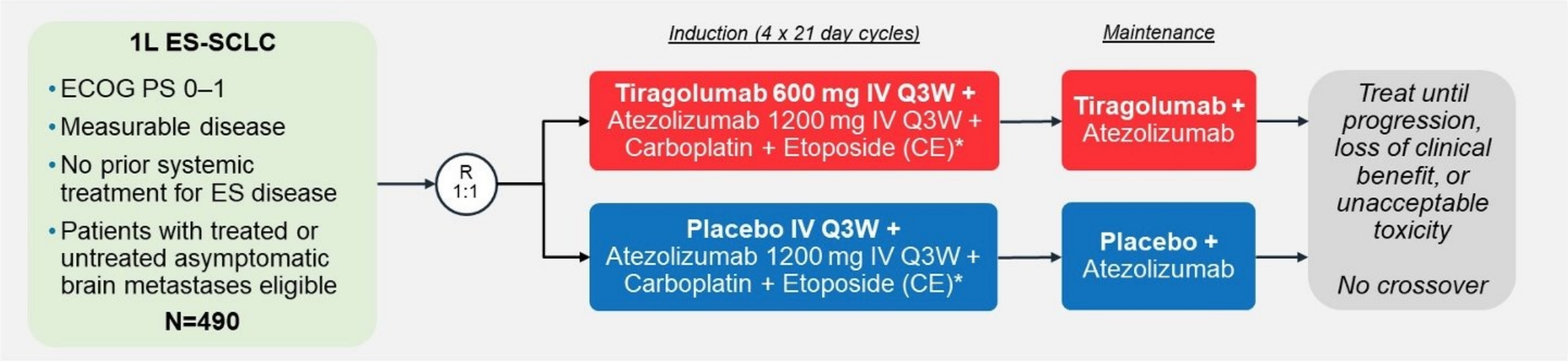
10.4 v 10.5 mo

HR 0.81 CI 0.67-0.97, p = 0.02

Paz-Ares L et al. ESMO Open. 2022 Apr; 7(2): 100408.

Adding More Checkpoint Inhibitors

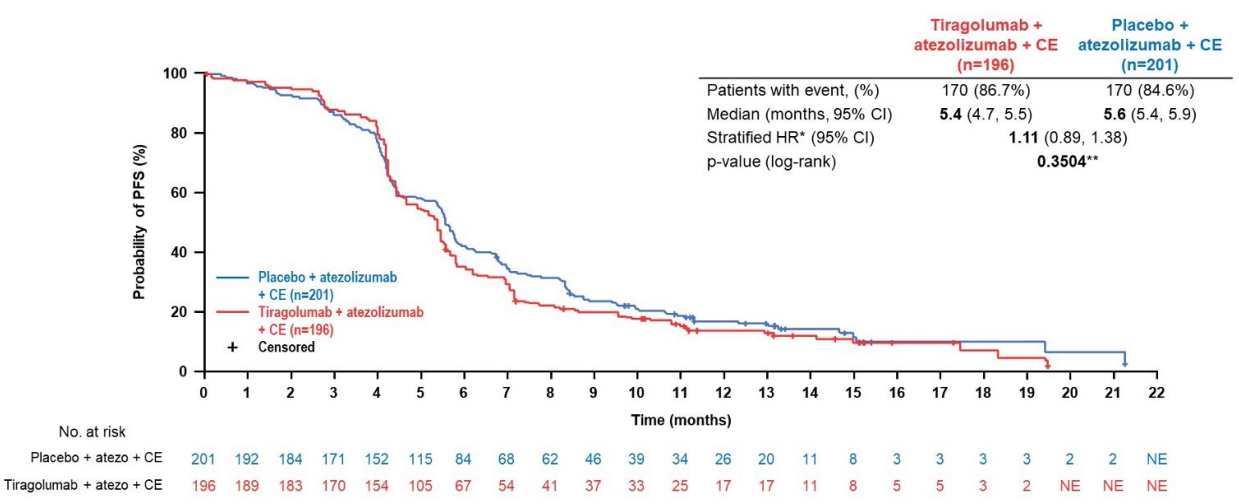
SKYSCRAPER-02: randomized, double-blind, placebo-controlled study of tiragolumab + atezolizumab + chemotherapy in patients with untreated ES-SCLC



Rudin C et al. ASCO. 2022

Tiragolumab Did Not Improve 1st Line Efficacy

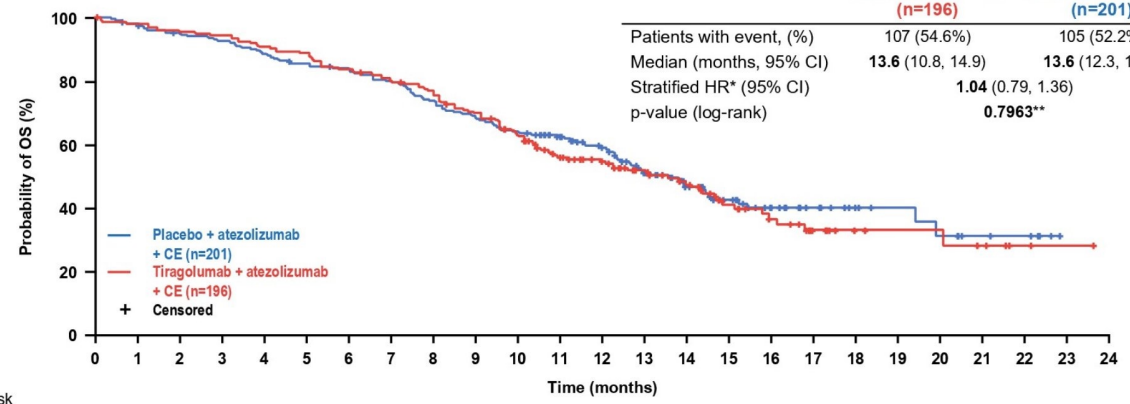
PFS: Primary Analysis Set



	Tiragolumab + atezolizumab + CE (n=196)	Placebo + atezolizumab + CE (n=201)
Patients with event, (%)	170 (86.7%)	170 (84.6%)
Median (months, 95% CI)	**5.4** (4.7, 5.5)	**5.6** (5.4, 5.9)
Stratified HR* (95% CI)	**1.11** (0.89, 1.38)	
p-value (log-rank)	**0.3504****	

No. at risk																							
Placebo + atezo + CE	201	192	184	171	152	115	84	68	62	46	39	34	26	20	11	8	3	3	3	3	2	2	NE
Tiragolumab + atezo + CE	196	189	183	170	154	105	67	54	41	37	33	25	17	17	11	8	5	5	3	2	NE	NE	NE

Interim OS: Primary Analysis Set



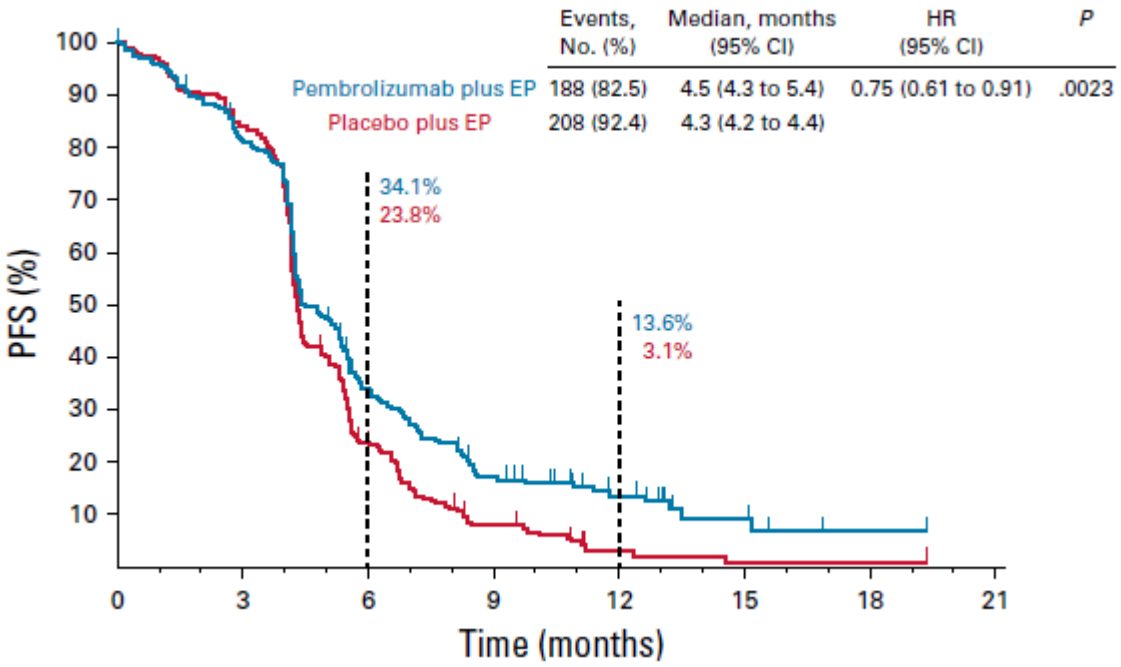
	Tiragolumab + atezolizumab + CE (n=196)	Placebo + atezolizumab + CE (n=201)
Patients with event, (%)	107 (54.6%)	105 (52.2%)
Median (months, 95% CI)	**13.6** (10.8, 14.9)	**13.6** (12.3, 15.2)
Stratified HR* (95% CI)	**1.04** (0.79, 1.36)	
p-value (log-rank)	**0.7963****	

No. at risk																							
Placebo + atezo + CE	201	195	188	183	175	168	164	156	144	134	125	115	97	70	47	36	26	19	12	9	7	5	4	NE	NE
Tiragolumab + atezo + CE	196	191	186	184	177	172	162	154	146	133	116	93	80	62	51	32	21	14	9	7	7	5	2	1	NE

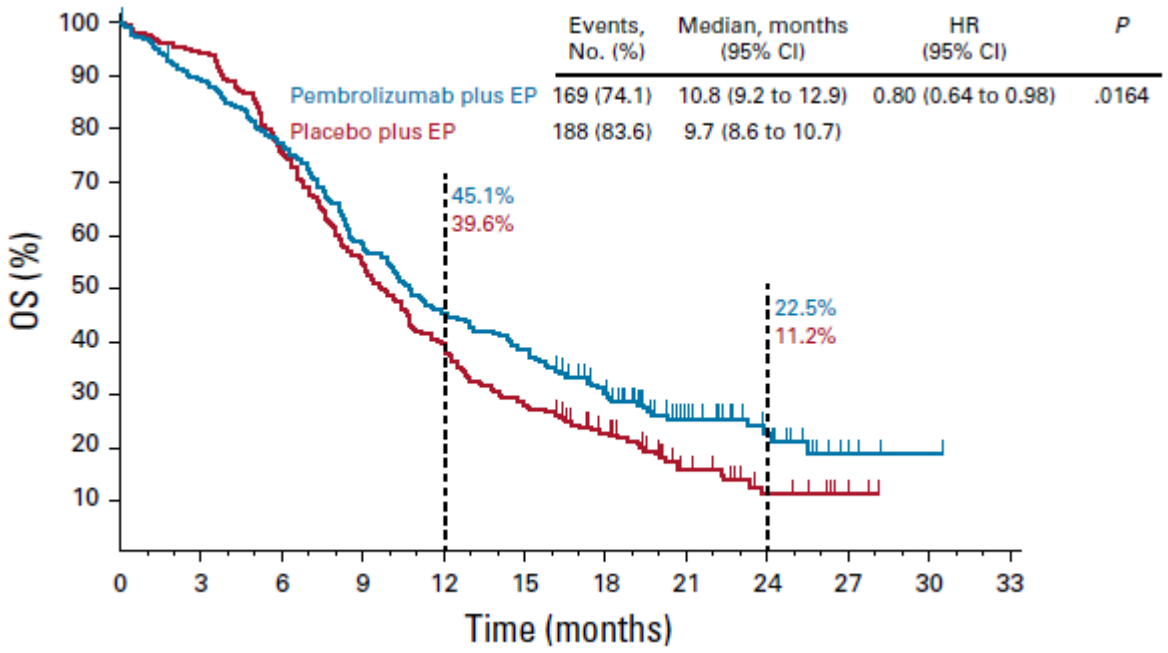
Rudin C et al. ASCO. 2022

KEYNOTE-604
Pembrolizumab + EP in ES SCLC

Improved PFS

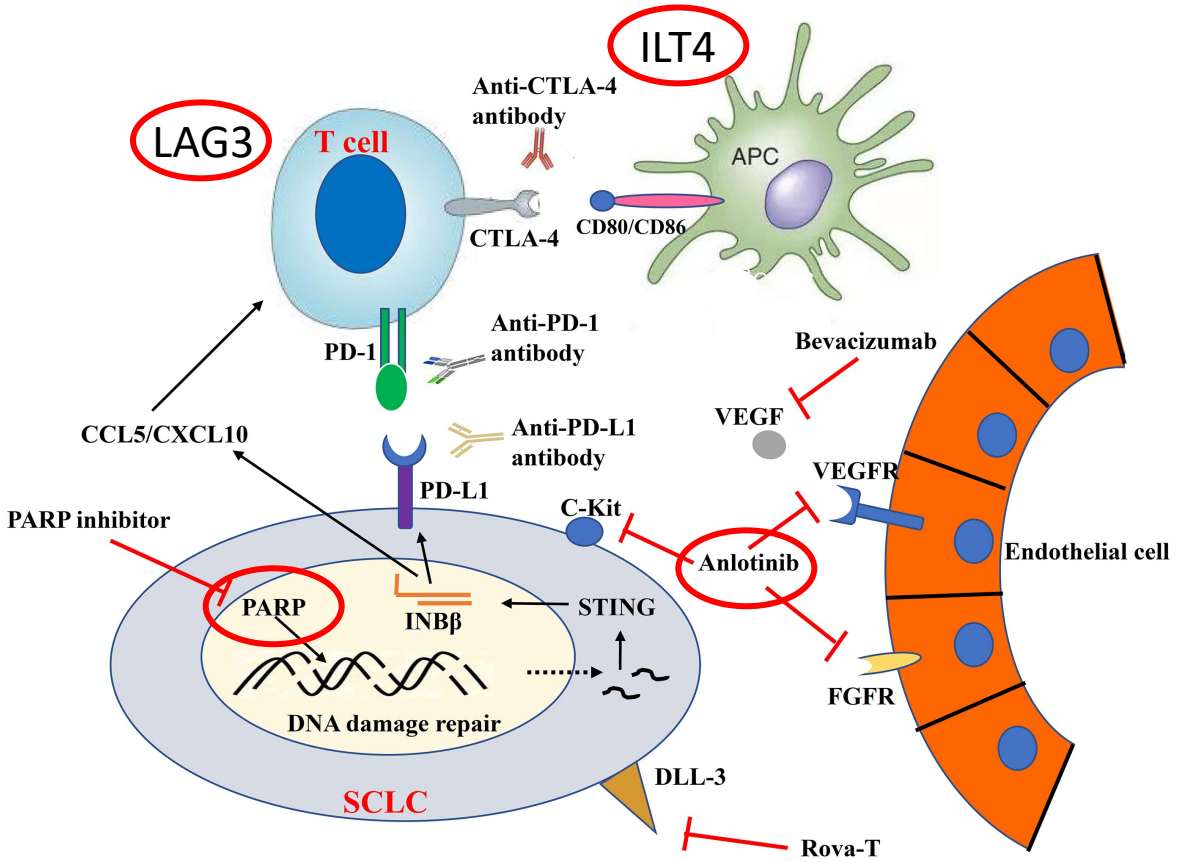


Did not improve OS



Rudin CM *et al.* J Clin Oncol 38:2369-2379. © 2020

Current 1st Line ES-SCLC Trial Landscape

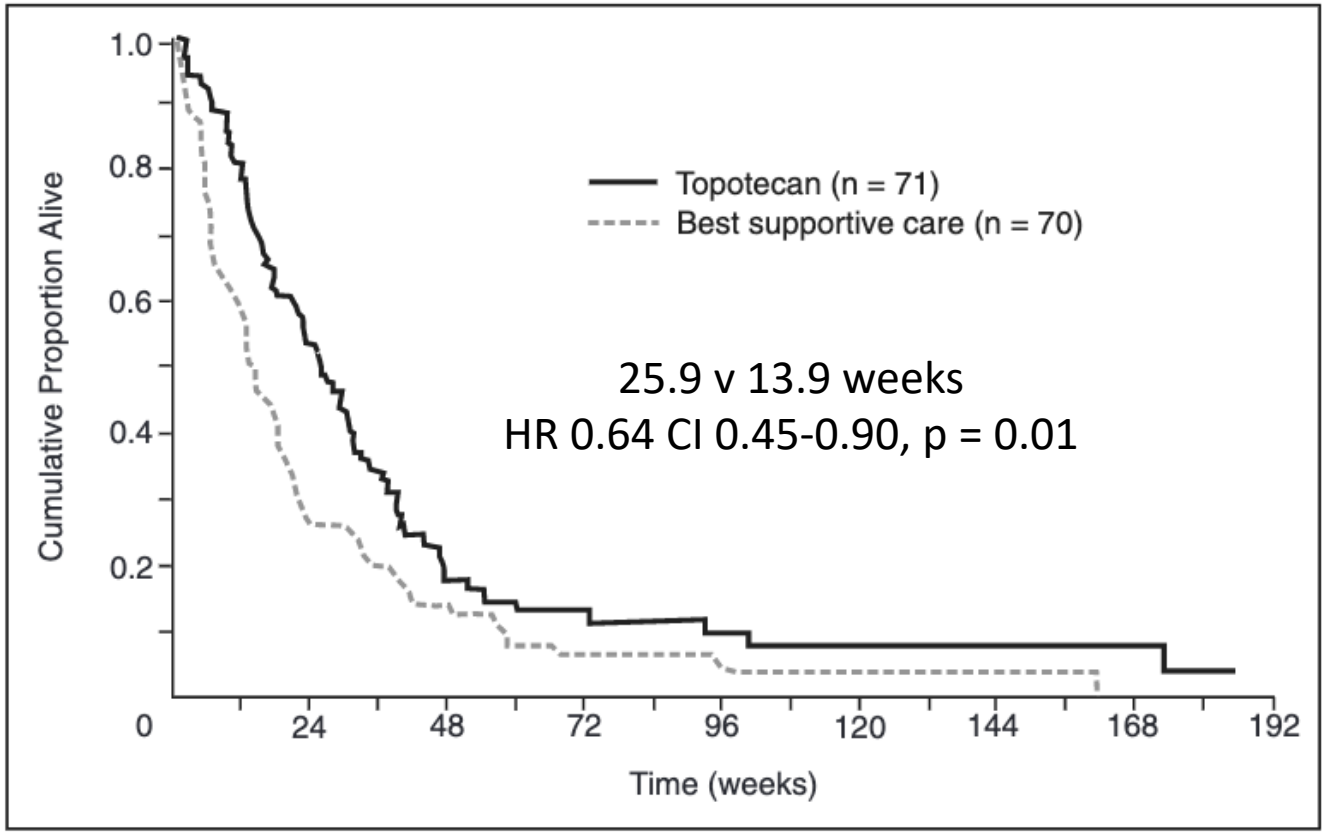


- EP + IO + anti-VEGF
  - Multiple trials + Anlotinib
  - VEGFR1, VEGFR2, VEGFR3, c-Kit, PDGFR-α, FGFR1, FGFR2, FGFR3
- EP + IO + other drugs
  - LAG3 –T cell inhibitor
  - ILT4 – MDSC activator
  - PARP inhibitors

Huang W *et al.* Translational Oncology, 2021-01-01, Volume 14, Issue 1, Article 100889, © 2020
Giunta EF *et al.* Front. Med., 25 May 2022

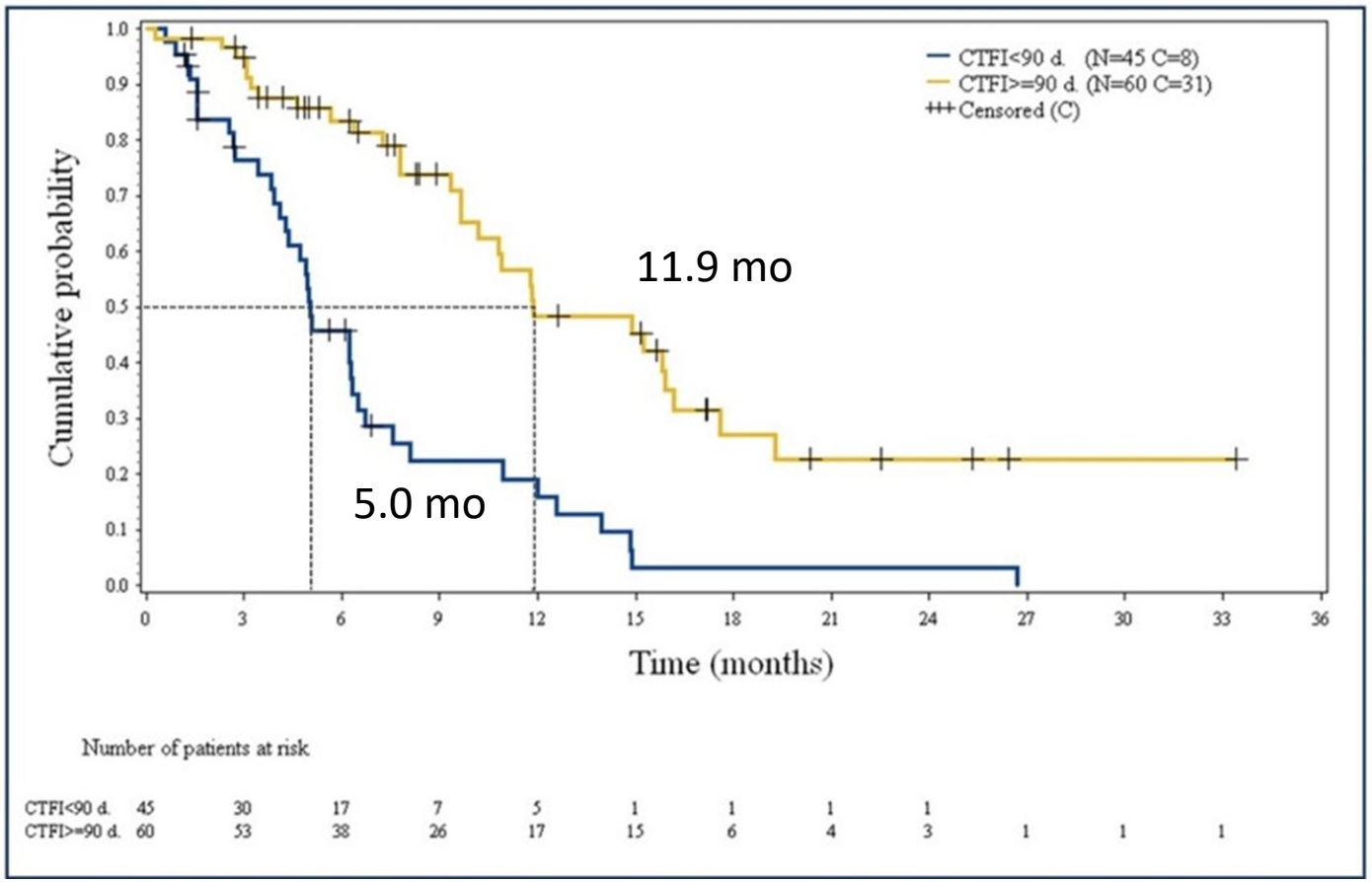
Subsequent Line Therapy ES SCLC

Second Line Topotecan



O'Brien *J Clin Oncol 2006 Dec 1;24(34):5441-7*

Lurbinectedin Phase 2 Basket Trial SCLC Cohort



	n	OS mo median (95% CI)	OS at 12 mo % (95% CI)	ORR
All	105	9.3 (6.3-11.8)	34.2 (23.2-45.1)	35%
Resistant CTFI< 90d	45	5.0 (4.1-6.3)	15.9 (3.6-28.2)	22%
Sensitive CTFI≥ 90d	60	11.9 (9.7-16.2)	48.3 (32.5-64.1)	45%

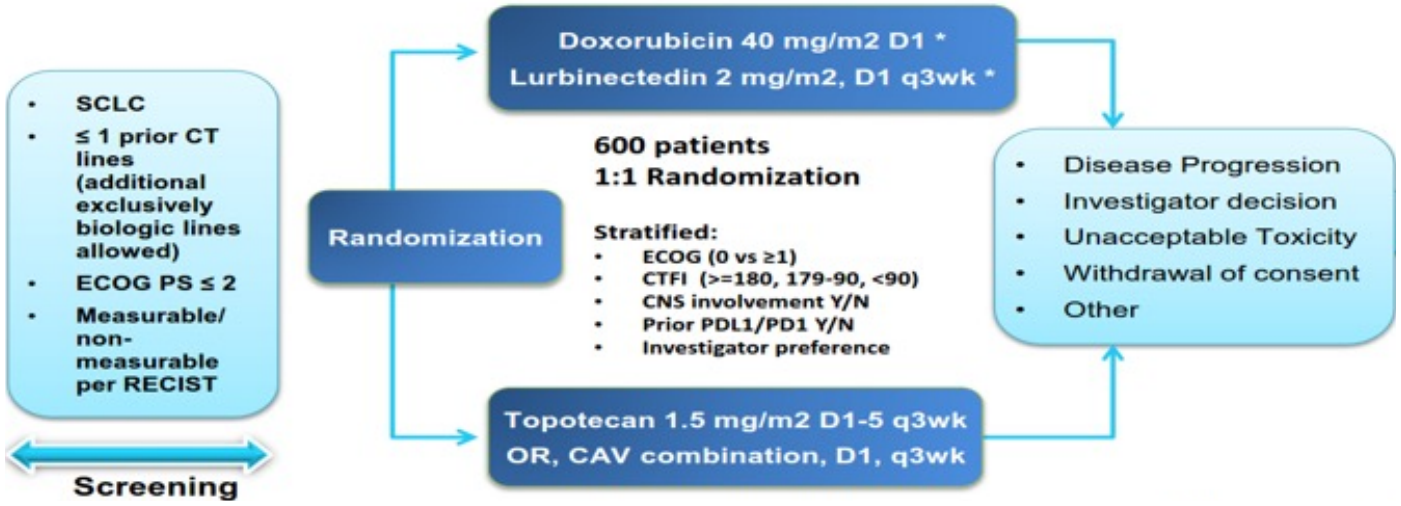
Topotecan

OS ~6.5 mo

RR ~20%

Paz-Ares LG et al. Meeting Abstract | 2019 ASCO Annual Meeting I
Scientific Reports volume 5, Article number: 15437 (2015)

ATLANTIS: Lurbinectedin + Doxorubicin



- 613 patients
- Lurbinectedin 2mg/m^2 + Doxorubicin vs Topotecan or CAV

- Median OS of 8.6 mo with the lurbinectedin vs. 7.6 mo
- Lower dose than Phase 2 basket trial (3.2 v 2.0 mg/m^2)
- Higher ORR than the control group (31.6% vs. 29.7%)
- Longer median duration of response (5.7 mo vs. 3.8 mo; HR = 0.58; 95% CI, 0.41-.81)

Trigo J et al. Lancet Oncol 2020; 21: 645–54

Lurbinectedin Clinical Trials

- LAGOON Phase 3 Trial For Single Agent vs Combination Lurbinectedin vs SOC
- Plan to enroll 705 patients
- 3 arm trial with lurbinectedin at single agent dosing 3.2 mg/m^2 or 2mg/m^2 with irinotecan, or control topotecan or irinotecan arms

- Lurbinectedin with Atezolizumab: NCT05091567, NCT04253145
- Lurbinectedin with Pembrolizumab: NCT04358237
- Nivolumab, ipilimumab and Lurbinectedin: NCT04610658
- Durvalumab plus Topotecan or Lurbinectedin: NCT04607954
- Safety and Efficacy of Lurbinectedin: NCT04894591

Novel Approaches In Development

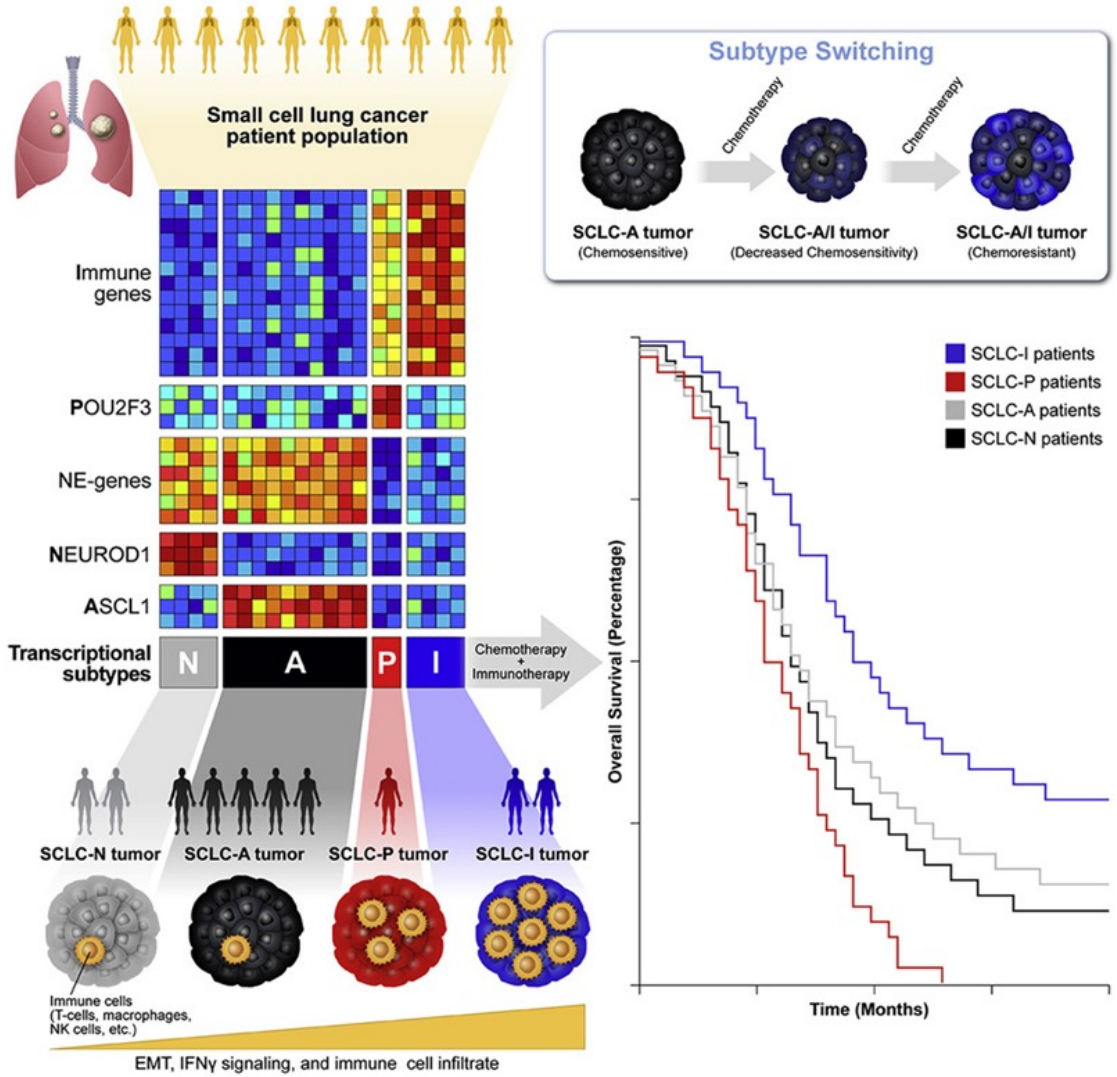
Targeting DLL3

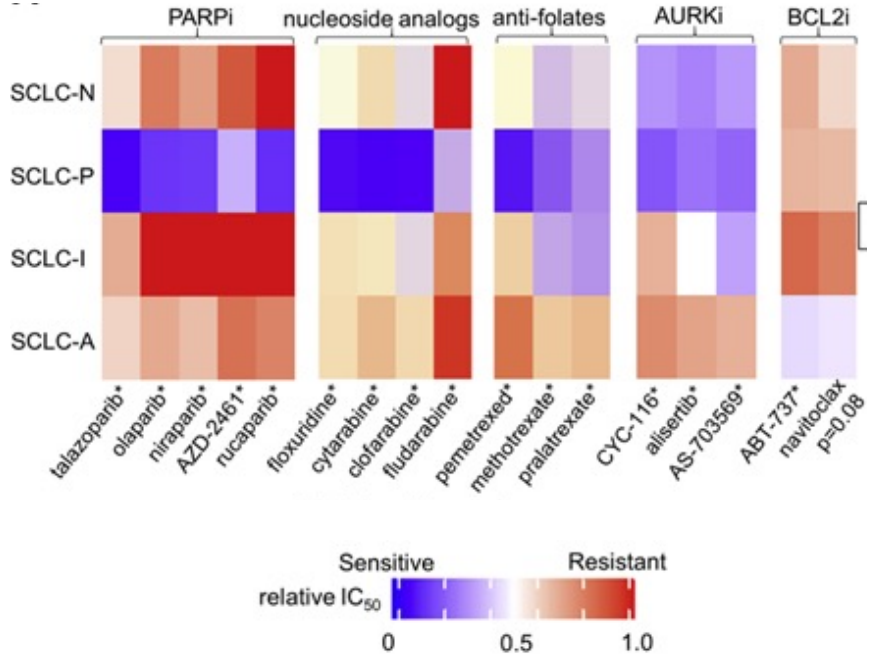
- Highly expressed in SCLC and low/no expression in normal tissue
- ADC
  - Rova-T
  - No benefit in 1st, 2nd or 3rd line trials

Was it the target or the delivery system?

- Bispecific T cell engagers (BiTE)
  - AMG 757
- CAR T therapy
  - AMG 119

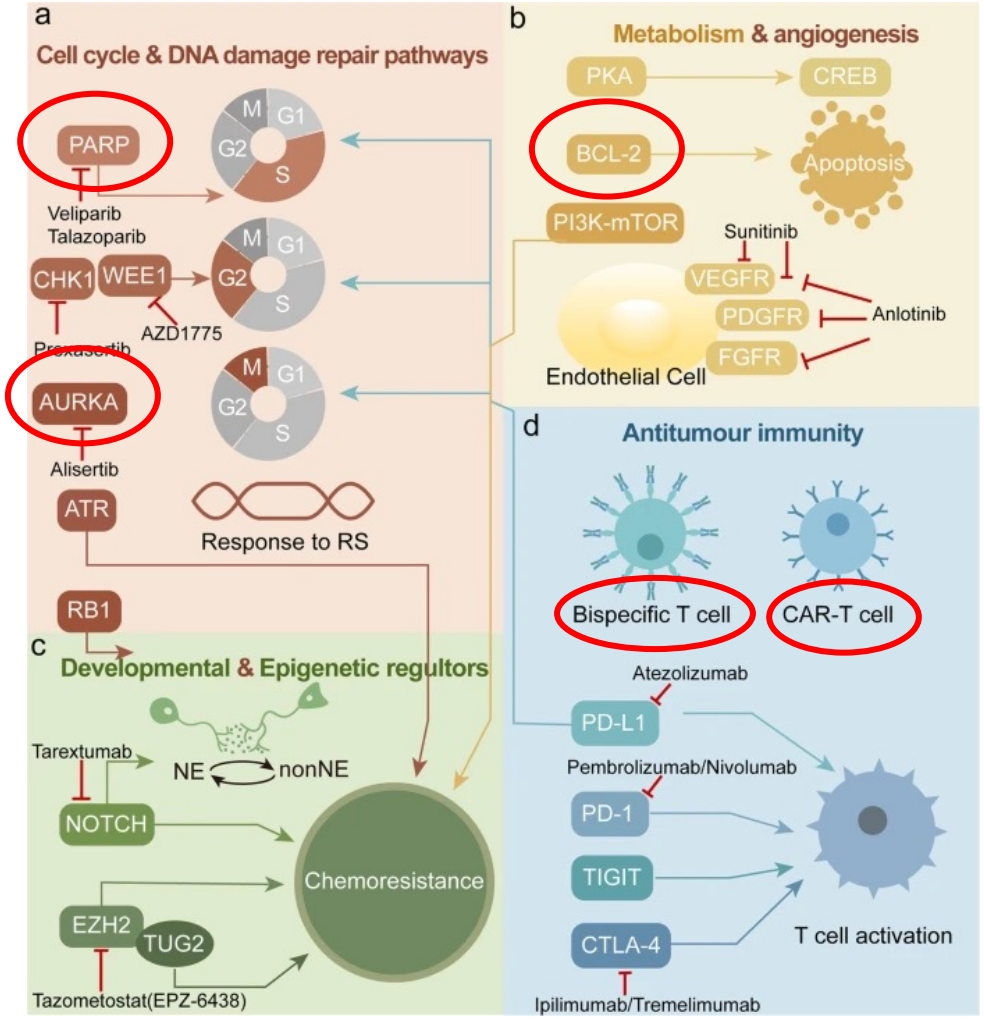
Future Directions – SCLC Subtypes





Gay C et al. *Cancer Cell* 2021 39346-360.e7DOI: (10.1016/j.ccell.2020.12.014)

Targeting SCLC Subtypes

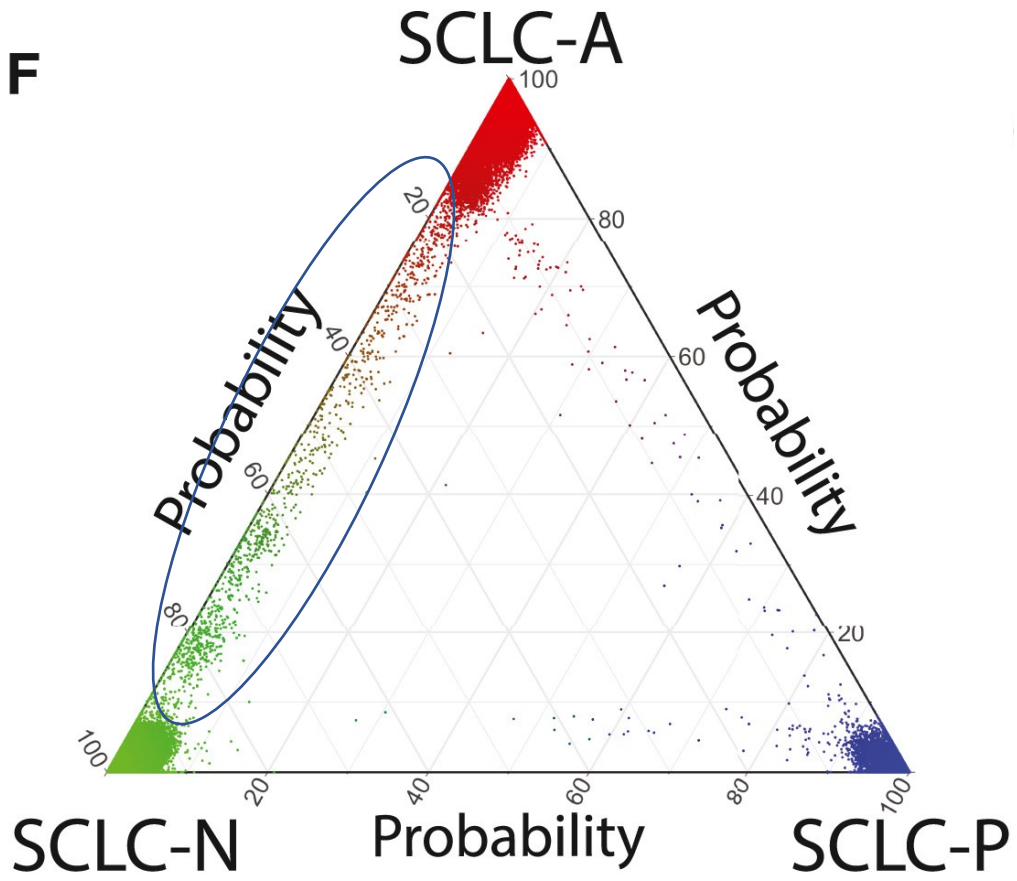


- <u>Emerging Clinical Trial Approaches</u>
- PARP inhibitors
  - Prevents DNA repair
- BCL-2/BCXL inhibitors
  - Promote apoptosis
- Aurora kinase inhibitors
  - Inhibit cell division

Signal Transduction and Targeted Therapy volume 7, Article number: 187 (2022)

Challenges in SCLC Subtype Targeting

- While morphologically homogenous, high levels of heterogeneity at the transcriptional level
- Tumor plasticity is a major problem
- Multiple pathways or underlying factors supporting plasticity may need to be targeted



Chan et al. Cancer Cell Vol 39, Issue 11, 8 November 2021

Conclusions

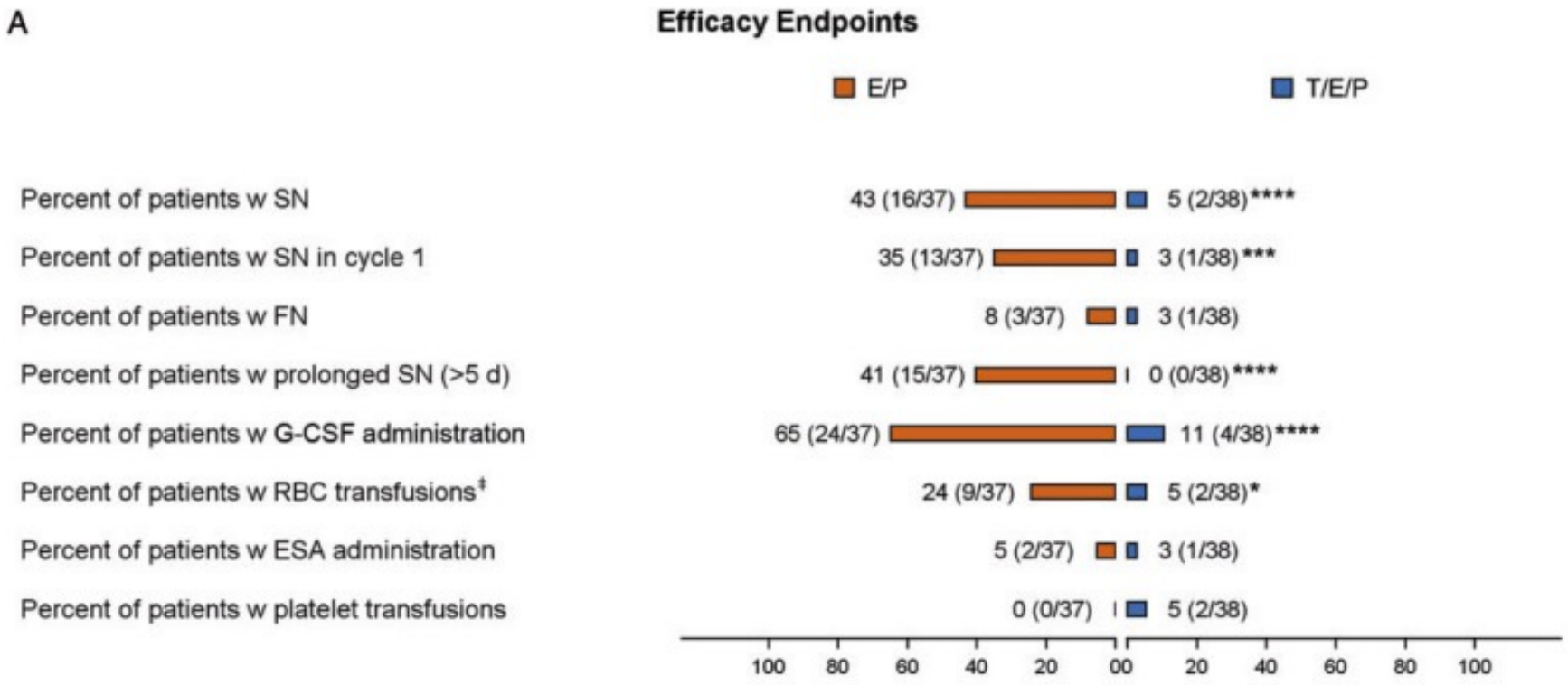
- The addition of anti PD-L1 therapy to 1st line ES-SCLC therapy is the first advance in decades
- Lurbinectedin is an available 2nd line therapy
  - LAGOON Phase III trial will clarify its role vs topotecan
- Subtyping of SCLC may provide better patient stratification for future precision therapy efforts

Questions & Discussion

Thank you!

Erin.Schenk@cuanschutz.edu

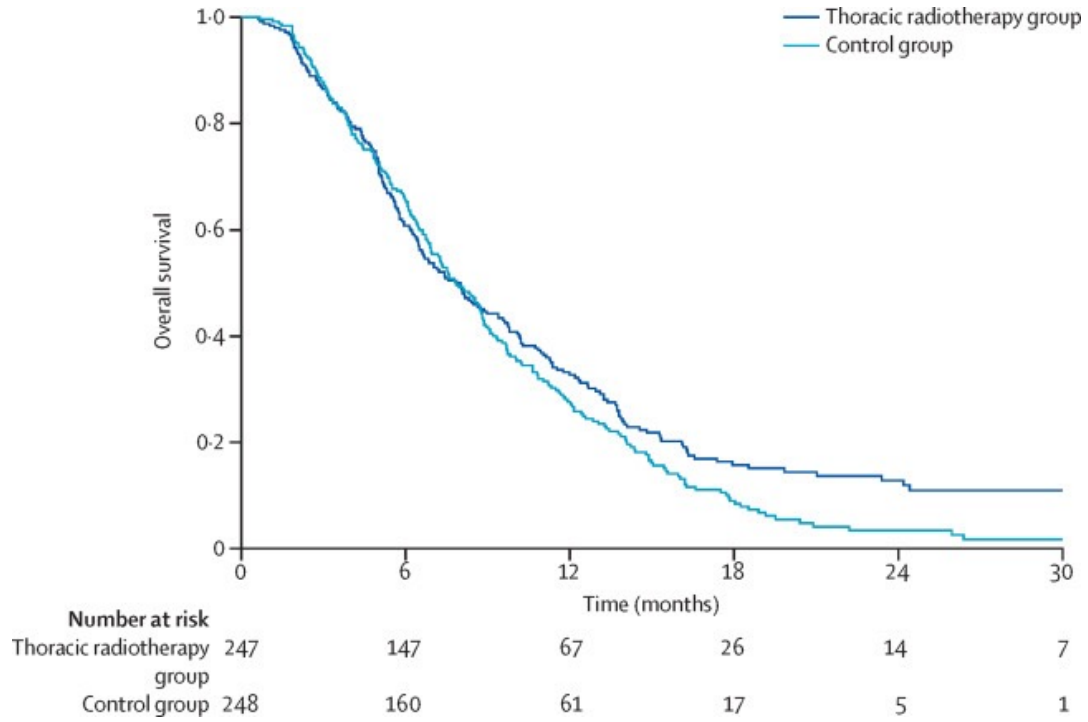
CDK4/6 inhibitor Trilaciclib



- Phase II study that randomized 77 patients to EP +/- trilaciclib

JM Weiss *et* al . Annals Oncology. VOL 30, ISSUE 10, P1613-1621, OCTOBER 01, 2019

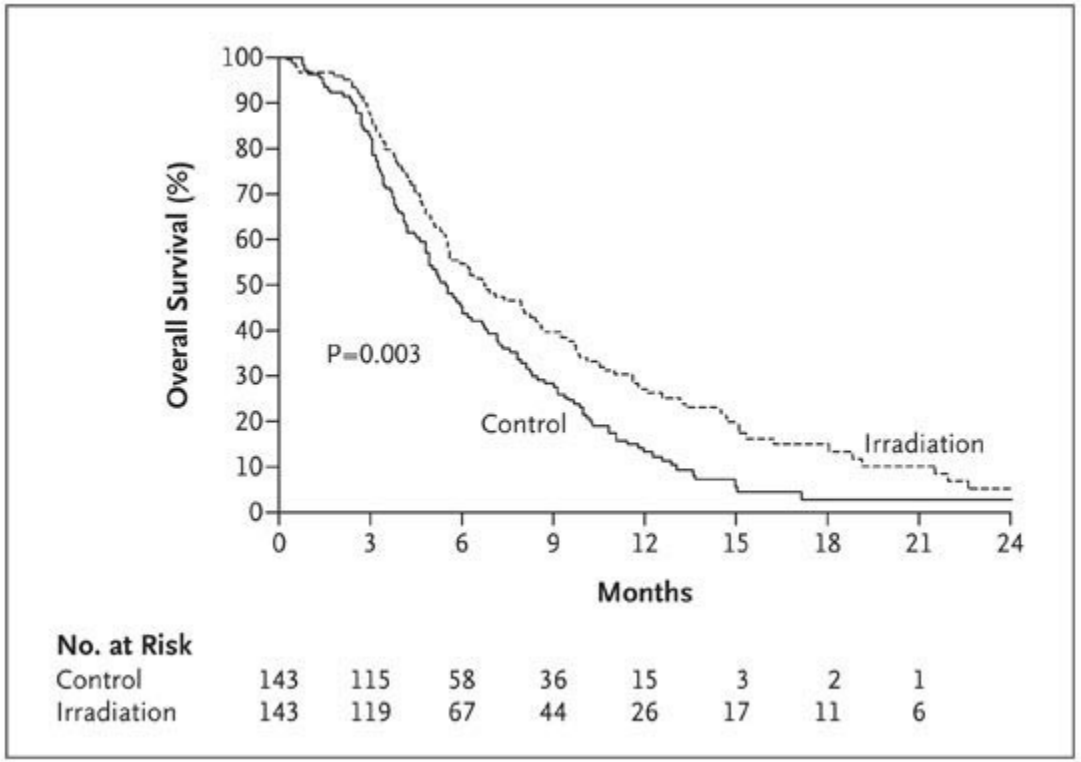
Consolidative Thoracic RT

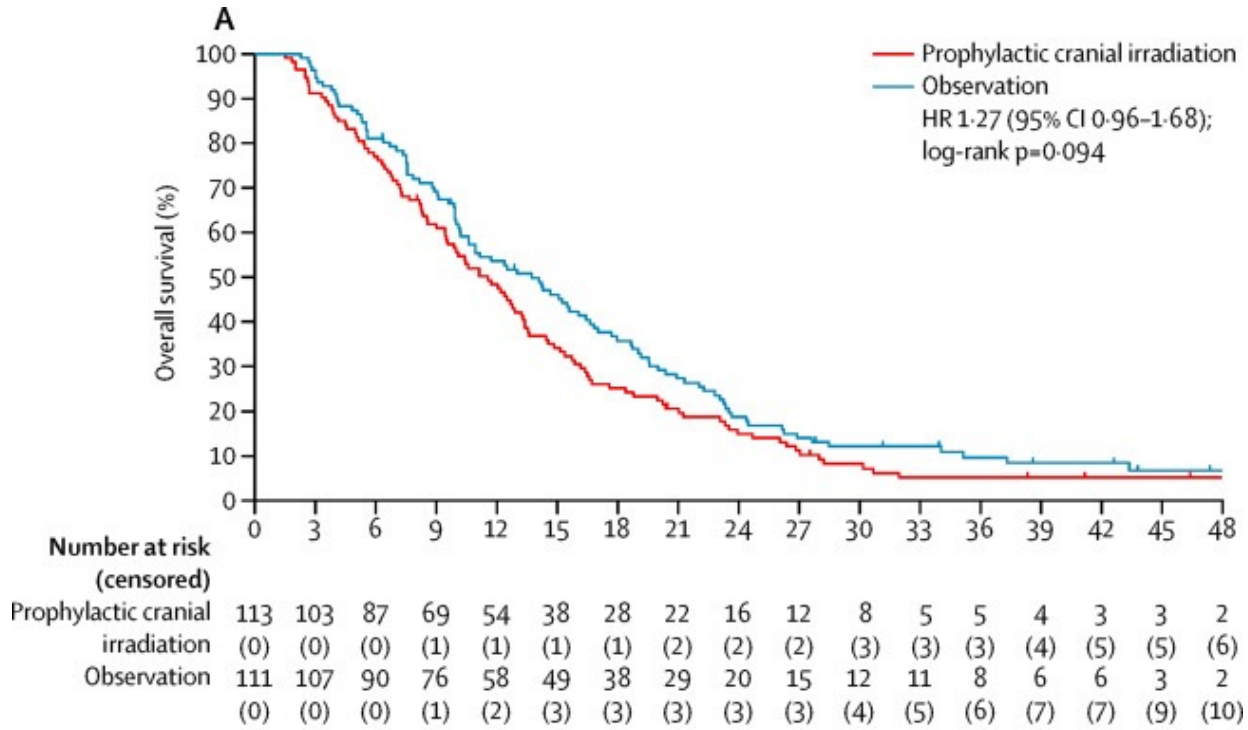


- 498 patients randomized after 4-6 cycles of chemotherapy
- 2 years, survival was 13% (95% CI 9–19) in the thoracic RT group and 3% (95% CI 2–8) in the control group (p=0·004).
- NNT to avoid one death was 10·6 (95% CI 6·1–42·5).

Slotman B *et al.* The Lancet. Volume 385, Issue 9962, 3–9 January 2015, Pages 36-42

PCI in ES-SCLC





Slotman B *et al.* August 16, 2007 N Engl J Med 2007; 357:664-672
Takahashi T *et al.* Lancet Oncology. Volume 18, Issue 5, May 2017, Pages 663-671