Society for Immunotherapy of Cancer

Advances in Cancer Immunotherapy™

New Directions and SCLC Treatment

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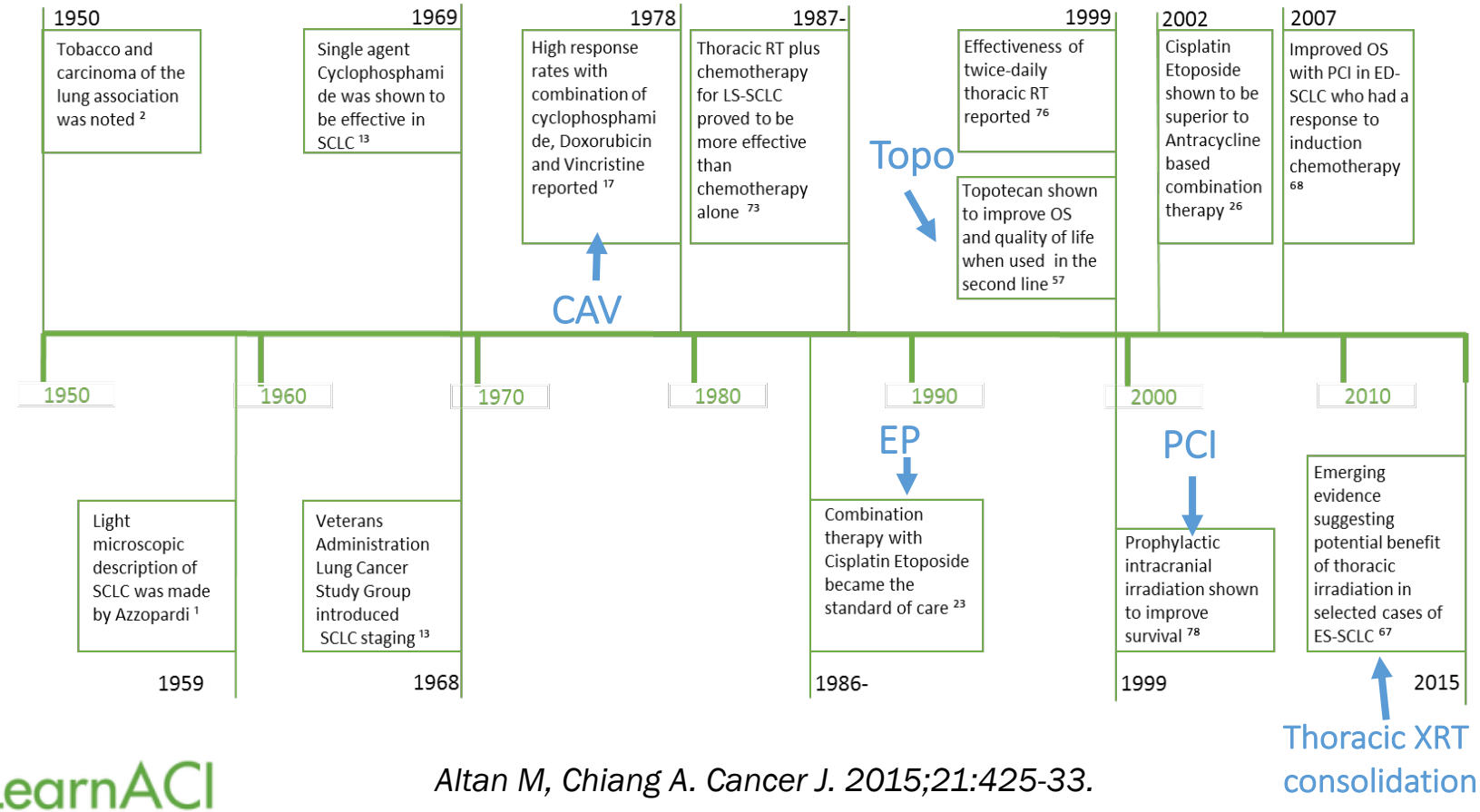
Disclosures

- Advisory Boards: AstraZeneca, Regeneron/Sanofi
- Research: BMS, AstraZeneca, AbbVie
- I will not be discussing non-FDA approved indications during my presentation.

From 1960 to 2018: Milestones in SCLC Chemotherapy and Radiation Approaches



Landscape is changing NOW…
with immunotherapy and advances in understanding SCLC biology

Altan M, Chiang A. Cancer J. 2015;21:425-33.

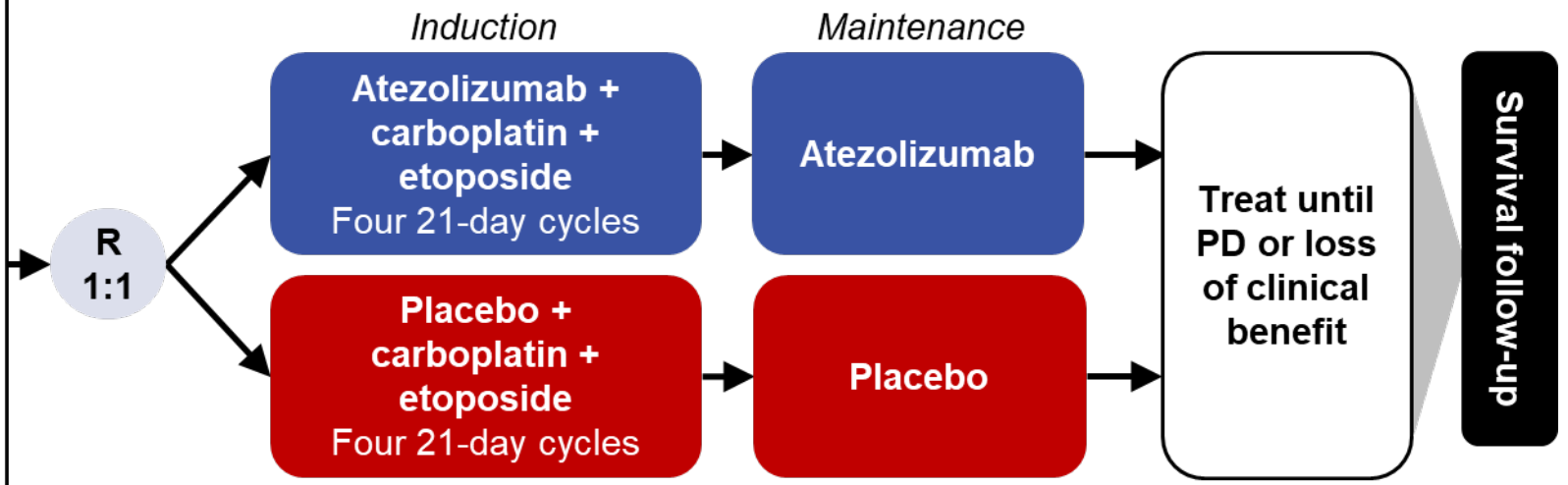
IMpower133: Atezolizumab + Carboplatin/Etoposide

- Measurable ES-SCLC (per RECIST version 1.1)
- ECOG PS 0 or 1
- No prior systemic treatment for ES-SCLC
- Patients with treated asymptomatic brain metastases were eligible

Stratification

- Sex (male vs female)
- ECOG PS (0 vs 1)
- Brain metastases (yes vs no)

N=403



Primary endpoints

- ✓ OS
- ✓ Investigator-assessed PFS

- *Liu SV, et al. J Clin Oncol. 2021;39:619-630.*

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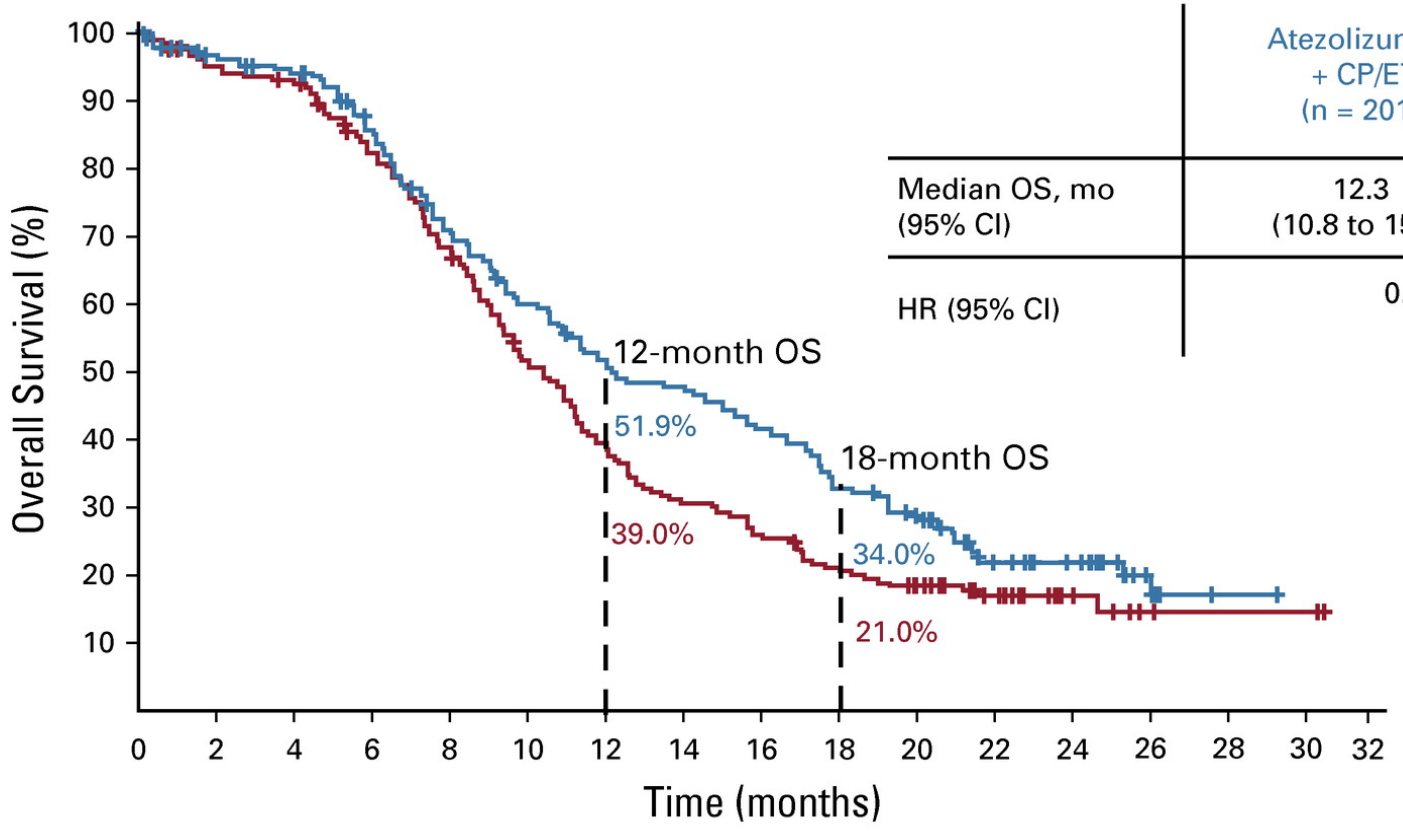
IMpower133: Atezolizumab + Carboplatin/Etoposide



	Atezolizumab + CP/ET (n = 201)	Placebo + CP/ET (n = 202)
Median OS, mo (95% CI)	12.3 (10.8 to 15.8)	10.3 (9.3 to 11.3)
HR (95% CI)	0.76 (0.60 to 0.95) *P* = .0154*	

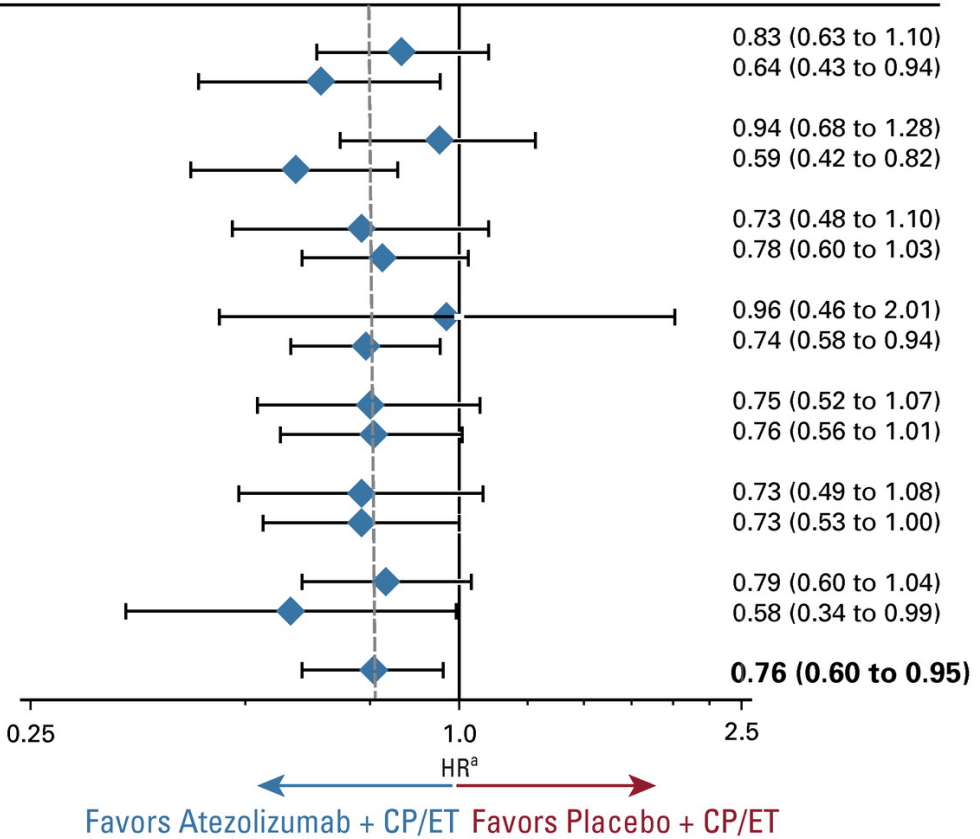
No. of Patients at Risk

Atezolizumab + CP/ET	201	187	180	159	130	109	93	86	75	61	51	28	21	8	1	
Placebo + CP/ET	202	189	183	160	131	97	74	58	49	39	33	20	8	3	2	2

- *Median follow up 22.9 months.*
  CP/ET, carboplatin plus etoposide.
  Liu SV, et al. J Clin Oncol. 2021;39:619-630.

IMpower133: Atezolizumab + Carbo/Etoposide

Subgroup	Median OS (months) Atezolizumab + CP/ET	Median OS (months) Placebo + CP/ET	OS HR[a] (95% CI)
Male (n = 261)	12.2	10.9	0.83 (0.63 to 1.10)
Female (n = 142)	13.6	9.5	0.64 (0.43 to 0.94)
< 65 years (n = 217)	12.1	11.5	0.94 (0.68 to 1.28)
≥ 65 years (n = 186)	14.4	9.6	0.59 (0.42 to 0.82)
ECOG PS 0 (n = 140)	16.8	12.6	0.73 (0.48 to 1.10)
ECOG PS 1 (n = 263)	11.3	9.3	0.78 (0.60 to 1.03)
Brain metastases (n = 35)	8.5	9.7	0.96 (0.46 to 2.01)
No brain metastases (n = 368)	12.6	10.4	0.74 (0.58 to 0.94)
Liver metastases (n = 149)	9.3	7.8	0.75 (0.52 to 1.07)
No liver metastases (n = 254)	16.3	11.2	0.76 (0.56 to 1.01)
bTMB < 10 (n = 134)	11.8	9.4	0.73 (0.49 to 1.08)
bTMB ≥ 10 (n = 212)	14.9	11.2	0.73 (0.53 to 1.00)
bTMB < 16 (n = 266)	12.5	10.0	0.79 (0.60 to 1.04)
bTMB ≥ 16 (n = 80)	17.1	11.9	0.58 (0.34 to 0.99)
ITT (N = 403)	**12.3**	**10.3**	**0.76 (0.60 to 0.95)**



IMpower133: Safety and Adverse Events

- **Atezolizumab vs Placebo Arms:**
- **TRAEs**
  - G3/4: 57.1% vs 56.1%
  - G5: 1.5% vs 1.5%
  - Atezolizumab or placebo-related
  - G3/4: 57% vs 56%
  - G5: 1.5% vs 1.5%
- **Maintenance atezolizumab treatment duration, median:**
  - 4.7 vs 4.1 mo
- **Total cumulative atezolizumab dose:**
  - 8400 mg (7 doses) vs 0

TABLE 1. Safety Summary and Drug Exposure

Category	Atezolizumab Plus CP/ET (N = 198)	Placebo Plus CP/ET (N = 196)
Number of AEs, n	2291	1919
All-cause AEs, n (%)		
Any-grade AEs	198 (100)	189 (96.4)
Grade 3 or 4	134 (67.7)	124 (63.3)
Grade 5	4 (2.0)	11 (5.6)
Serious AEs	77 (38.9)	69 (35.2)
Leading to any treatment withdrawal	24 (12.1)	6 (3.1)
Leading to any dose modification or interruption	139 (70.2)	119 (60.7)
Atezolizumab or placebo	118 (59.6)	102 (52.0)
Treatment-related AEs, n (%)		
Any-grade AEs	188 (94.9)	181 (92.3)
Atezolizumab or placebo-related	130 (65.7)	100 (51.0)
Grade 3 or 4	113 (57.1)	110 (56.1)
Grade 5	3 (1.5)	3 (1.5)
AESIs, n (%)*		
Any-grade	82 (41.4)	48 (24.5)
Grade 3 or 4	16 (8.1)	5 (2.6)
Serious	14 (7.1)	7 (3.6)
Treatment-related	66 (33.3)	36 (18.4)
Grade 3 or 4	14 (7.1)	4 (2.0)
Serious	12 (6.1)	5 (2.6)
Leading to any treatment withdrawal	8 (4.0)	2 (1.0)
Leading to any dose modification or interruption	24 (12.1)	11 (5.6)
Treated with steroids or hormone replacement therapy†	40 (20.2)	11 (5.6)

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Liu SV, et al. J Clin Oncol. 2021;39:619-630.

Atezolizumab Immune-Related Adverse Events

irAE	Atezolizumab Group (n = 198)		Placebo Group (n = 196)	
	All grades	Grades 3 to 4	All grades	Grades 3 to 4
Rash	37 (18.7%)	4 (2.0%)	20 (10.2%)	0
Hypothyroidism	25 (12.6%)	0	1 (0.5%)	0
Hepatitis	14 (7.1%)	3 (1.5%)	9 (4.6%)	0
Infusion-related reaction	11 (5.6%)	4 (2.0%)	10 (5.1%)	1 (0.5%)
Hyperthyroidism	11 (5.6%)	0	5 (2.6%)	0
Pneumonitis	4 (2.0%)	1 (0.5%)	5 (2.6%)	2 (1.0%)
Colitis	3 (1.5%)	2 (1.0%)	0	0
Pancreatitis	1 (0.5%)	1 (0.5%)	2 (1.0%)	2 (1.0%)
Severe cutaneous reaction	2 (1.0%)	0	0	0
Adrenal insufficiency	0	0	2 (1.0%)	0
Rhabdomyolysis	2 (1.0%)	1 (0.5%)	0	0
Nephritis	1 (0.5%)	1 (0.5%)	1 (0.5%)	0
Hypophysitis	1 (0.5%)	0	0	0
Vasculitis	0	0	1 (0.5%)	0
Diabetes mellitus	1 (0.5%)	0	0	0
Guillain-Barre Syndrome	1 (0.5%)	1 (0.5%)	0	0

- irAE, immune-related AE.

Horn L, et al. N Engl J Med. 2018;379:2220-2229.

CASPIAN Study Design

Phase 3, Global, Randomized, Open-Label, Active-Controlled, Multicenter Study

- Treatment-naive ES-SCLC
- WHO PS 0 or 1
- Asymptomatic or treated and stable brain metastases permitted
- Life expectancy ≥ 12 weeks
- Measurable disease per RECIST v1.1

N = 805 (randomized)

1:1:1 R

Stratified by planned platinum (carboplatin vs cisplatin)

Durvalumab + EP* Q3W for 4 cycles	Durvalumab Q4W until PD
Durvalumab + tremelimumab + EP* Q3W for 4 cycles	Durvalumab‡ Q4W until PD
EP* Q3W for up to 6 cycles†	Optional PCI†

Primary endpoint
- OS

Secondary endpoints
- PFS§
- ORR§
- Safety & tolerability
- PROs

- Updated analysis of OS after median follow-up of approximately 3 years was a planned exploratory analysis
  - PFS and ORR data were not collected since the previous data cutoff
  - Serious AEs (including deaths) were analyzed, but other safety data were not collected

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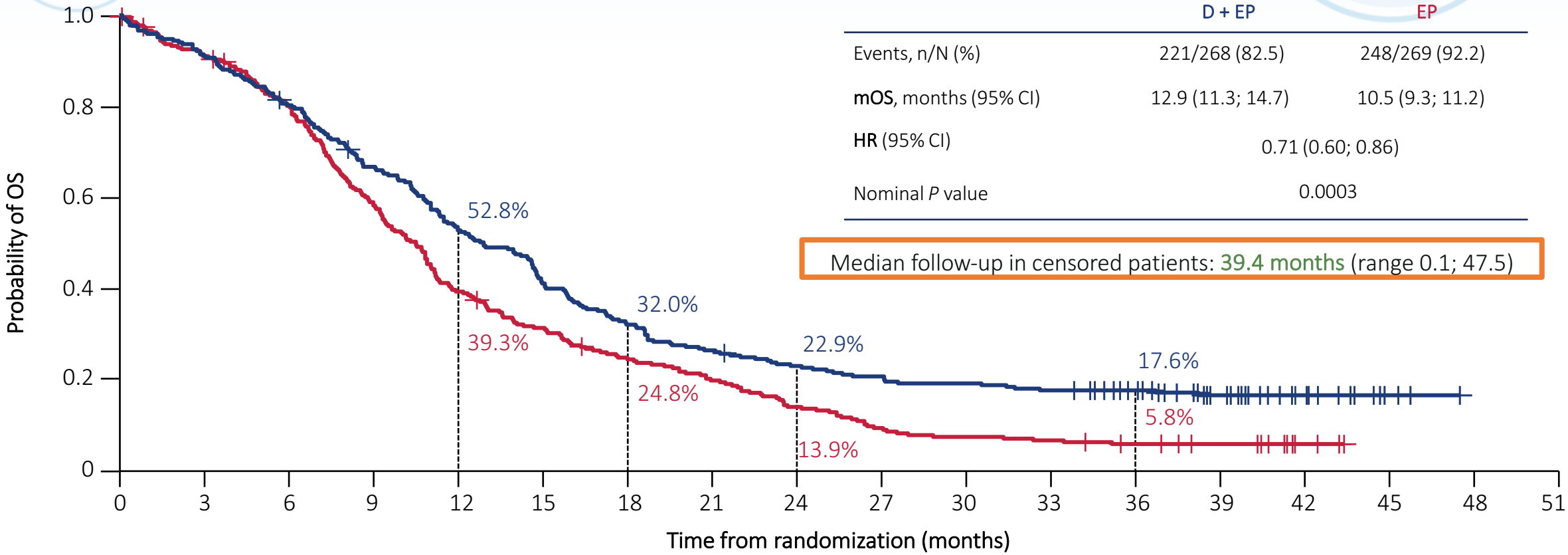
Paz-Ares LG, et al. Ann Oncol. 2021;32(suppl 5):S1283-S1346.

CASPIAN 3-Year OS Update: Durvalumab + EP vs EP



	D + EP	EP
Events, n/N (%)	221/268 (82.5)	248/269 (92.2)
mOS, months (95% CI)	12.9 (11.3; 14.7)	10.5 (9.3; 11.2)
HR (95% CI)	0.71 (0.60; 0.86)	
Nominal *P* value	0.0003	

Median follow-up in censored patients: 39.4 months (range 0.1; 47.5)

No. at risk

D + EP	268	244	214	177	140	109	85	70	60	54	50	46	39	25	13	3	0	0
EP	269	243	212	156	104	82	64	51	36	24	19	17	13	10	3	0	0	0

Data cutoff: March 22, 2021.

Paz-Ares LG, et al. Ann Oncol. 2021;32(suppl 5):S1283-S1346.

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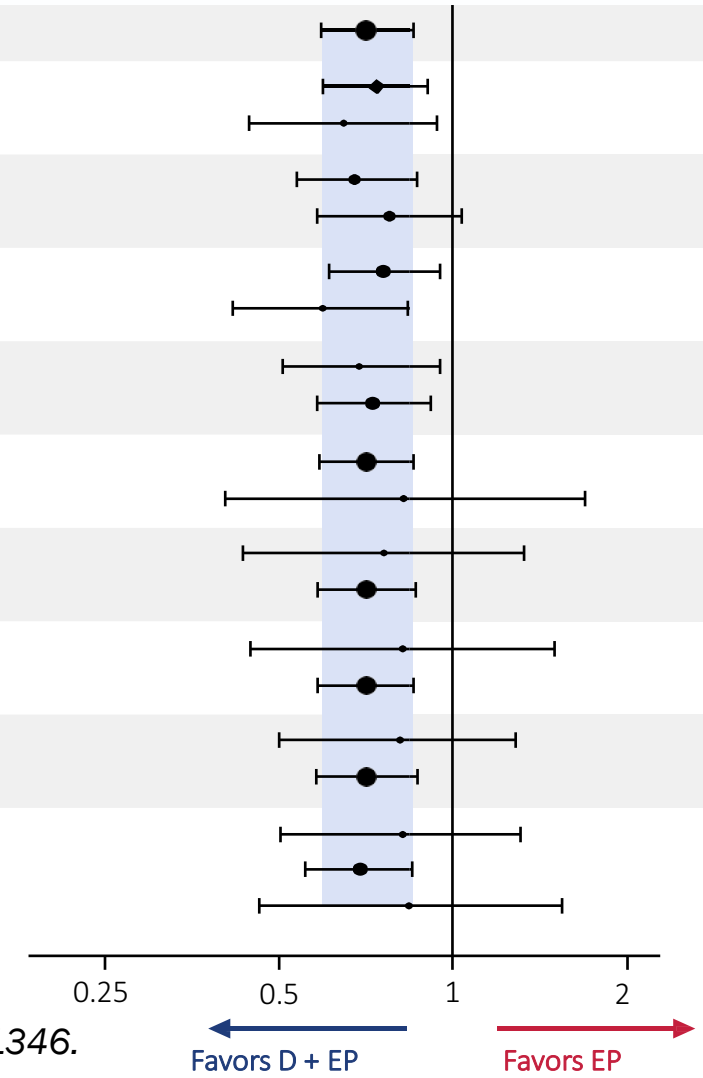
3-Year OS Update: Durva/EP vs EP; Subgroup Analysis

		HR (95% CI)
All patients (n = 537)		0.71 (0.60; 0.86)
Planned platinum agent	Carboplatin (n = 402)	0.74 (0.60; 0.91)
	Cisplatin (n = 135)	0.65 (0.45; 0.94)
Age	< 65 years (n = 324)	0.68 (0.54; 0.87)
	≥ 65 years (n = 213)	0.78 (0.59; 1.04)
Sex	Male (n = 374)	0.76 (0.62; 0.95)
	Female (n = 163)	0.60 (0.42; 0.84)
Performance status	0 (n = 189)	0.70 (0.51; 0.95)
	1 (n = 348)	0.73 (0.58; 0.92)
Smoking status	Smoker (n = 500)	0.71 (0.59; 0.86)
	Nonsmoker (n = 37)	0.82 (0.41; 1.69)
Brain/CNS metastases	Yes (n = 55)	0.76 (0.43; 1.33)
	No (n = 482)	0.71 (0.59; 0.86)
AJCC disease stage at diagnosis	Stage III (n = 52)	0.82 (0.45; 1.49)
	Stage IV (n = 485)	0.71 (0.59; 0.86)
Race	Asian (n = 78)	0.81 (0.50; 1.28)
	Non-Asian (n = 458)	0.71 (0.58; 0.87)
Region	Asia (n = 76)	0.82 (0.51; 1.31)
	Europe (n = 405)	0.69 (0.56; 0.85)
	North and South America (n = 56)	0.84 (0.46; 1.54)



Data cutoff: March 22, 2021.

Paz-Ares LG, et al. Ann Oncol. 2021;32(suppl 5):S1283-S1346.

Serious AEs: 3-Year Update

	D + EP (n = 265)	EP (n = 266)
Serious AEs (all cause), n (%)*	86 (32.5)	97 (36.5)
Febrile neutropenia	12 (4.5)	12 (4.5)
Pneumonia	6 (2.3)	11 (4.1)
Anemia	5 (1.9)	12 (4.5)
Thrombocytopenia	1 (0.4)	9 (3.4)
Hyponatremia	2 (0.8)	4 (1.5)
Neutropenia	2 (0.8)	7 (2.6)
Diarrhea	2 (0.8)	4 (1.5)
Pulmonary embolism	1 (0.4)	0
AEs leading to death (all cause), n (%)†	14 (5.3)	16 (6.0)
Treatment-related AEs leading to death	6 (2.3)	2 (0.8)

*Serious AEs occurring in ≥ 2% of patients in any treatment arm are shown. †Four additional deaths were reported since the previous analysis (none treatment related): 1 in the D+EP arm (aspiration), 2 in the D+T+EP arm (drowning and *pneumocystis jirovecii* pneumonia), and 1 in the EP arm (small intestine leiomyosarcoma). *Paz-Ares LG, et al. Ann Oncol. 2021;32(suppl 5):S1283-S1346.*

Durvalumab: Immune-Related Adverse Events

irAE (n = 265)	Durvalumab + EP n (%)		EP n (%)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Any	52 (20%)	12 (5%)	7 (3%)	1 (< 1%)
Hypothyroid events	24 (9%)	0	2 (1%)	0
Hyperthyroid events	14 (5%)	0	0	0
Pneumonitis	7 (3%)	2 (1%)	2 (1%)	1 (< 1%)
Hepatic events	7 (3%)	5 (2%)	0	0
Dermatitis/rash	4 (2%)	0	2 (1%)	0
Diarrhea/colitis	4 (2%)	1 (< 1%)	1 (< 1%)	0
Thyroiditis	4 (2%)	0	0	0
Type I diabetes mellitus	4 (2%)	4 (2%)	0	0
Adrenal insufficiency	1 (< 1%)	1 (< 1%)	0	0
Pancreatic events	1 (< 1%)	1 (< 1%)	0	0
Other rare (arthritis)	2 (1%)	0	0	0

Paz-Ares L, et al: 2019 World Conference on Lung Cancer. Abstract PL02.11. Presented September 9, 2019.

FDA Approvals for 1L ES-SCLC: Updated Analyses

	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
New Technology Add-on Payments (NTAP)	yes	yes

FDA Approvals for Relapsed SCLC

Lurbinectedin, approved June 2020

- N=105 patients
- ORR 35%
- Median DOR 5.3 months

Pembrolizumab, approved June 2019

NOW WITHDRAWN

- N=83
- ORR 19%, CR 2%
- Durable responses for ≥6 months in 94%, ≥12 months in 63%, and ≥18 months in 56% of the 16 responding patients

Nivolumab, approved Aug 2018

NOW WITHDRAWN

- N=109
- ORR 12%
- Responses durable for ≥6 months in 77%, ≥12 months in 62%, and ≥18 months in 39% of the 13 responding patients

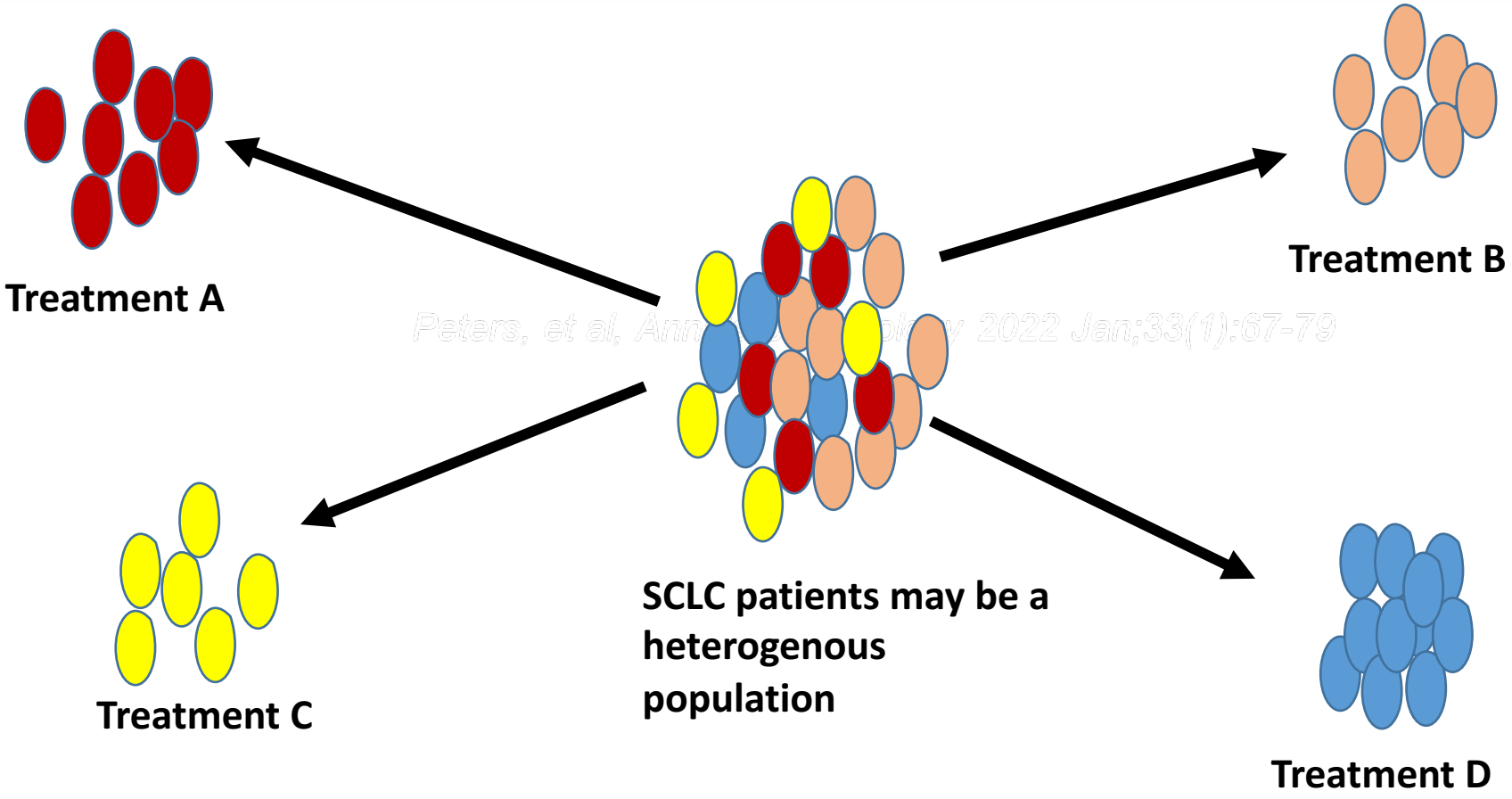
PRINCIPLES OF SYSTEMIC THERAPY

Consider dose reduction or growth factor support for patients with PS 2.

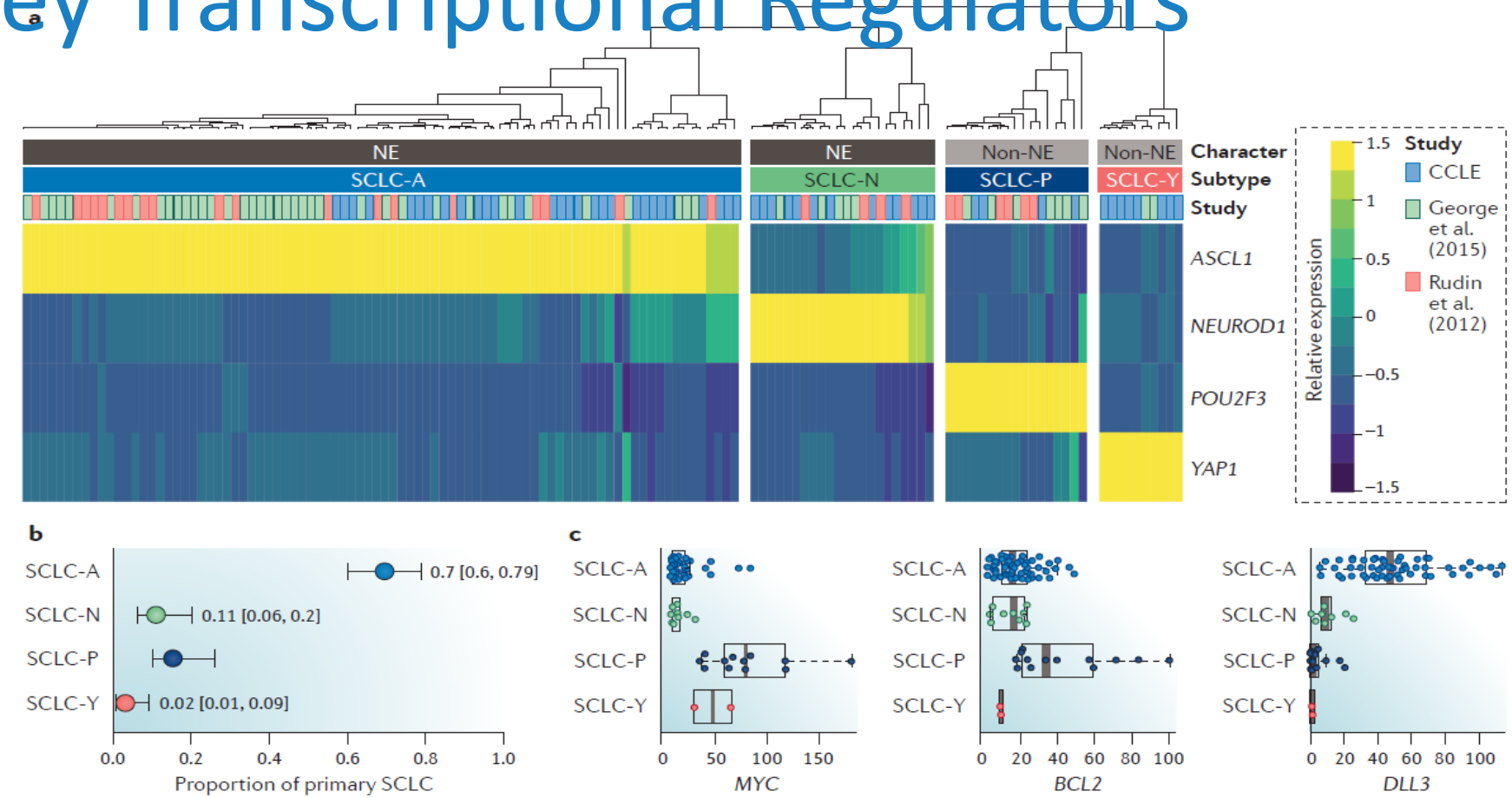
SCLC SUBSEQUENT SYSTEMIC THERAPY:[c]
Relapse ≤6 months PS 0–2
Preferred Regimens • Topotecan PO or IV[14-16] • Lurbinectedin[37] • Clinical trial Other Recommended Regimens • Paclitaxel[22,23] • Docetaxel[24] • Irinotecan[25] • Temozolomide[26,27] • Cyclophosphamide/doxorubicin/vincristine (CAV)[14] • Oral etoposide[28,29] • Vinorelbine[30,31] • Gemcitabine[32,33] • ~~Bendamustine (category 2B)~~[34] • Nivolumab[b,d,17,18] (category 3) • Pembrolizumab[b,d,19,20,21] (category 3)
Relapse >6 months
Preferred Regimens • Original regimen[d,35,36] Other Recommended Regimen • Lurbinectedin[37]

NCCN Clinical Practice Guidelines in Oncology. Small Cell Lung Cancer. V1.2022

SCLC: Is Targeted Therapy the Future?

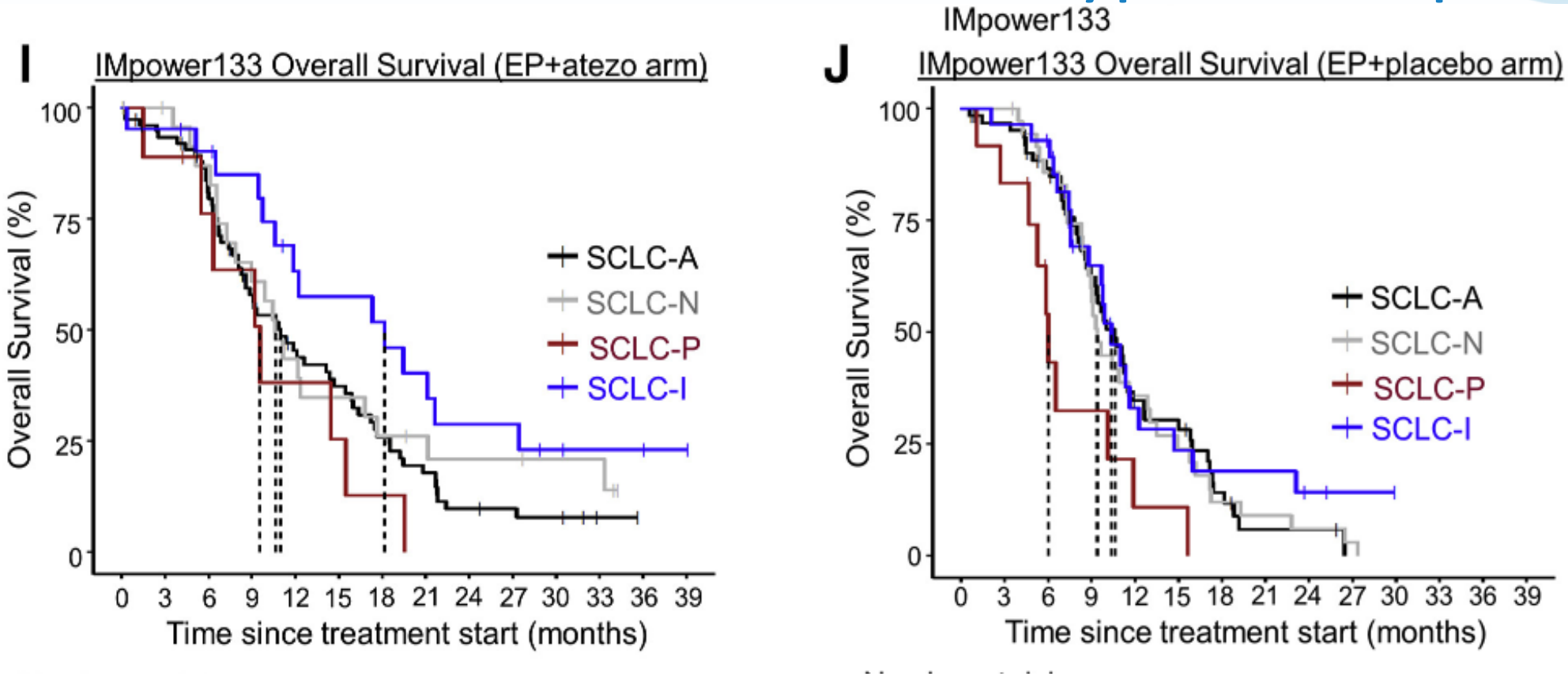


SCLC Biology: Molecular Subtypes by Expression of Key Transcriptional Regulators



Rudin C et al, Nature Reviews Cancer 2019:19;289-297

Better OS for SCLC-I "Inflamed Subtype" in IMpower 133



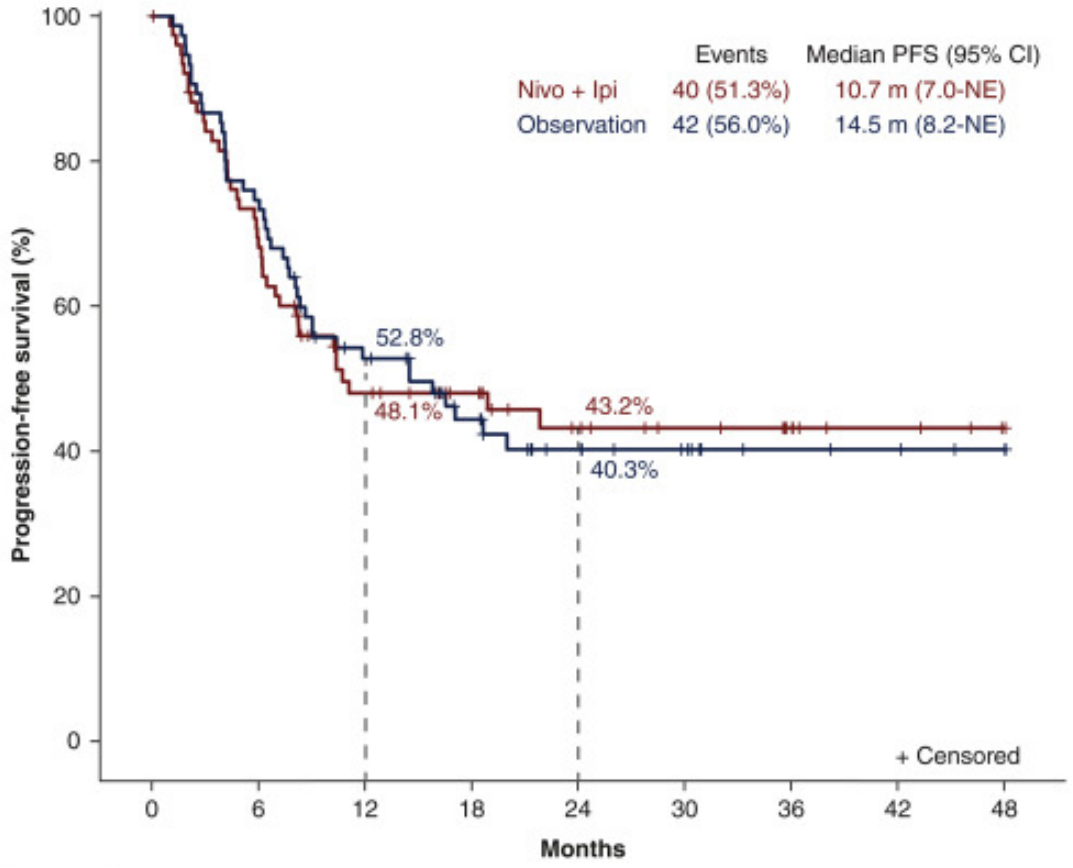
Gay, et al. Cancer Cell 2021 Mar 8;39(3):346-360

Phase II/III Immunotherapy Trials in Limited Stage SCLC: Consolidation following chemoradiation

Toripalimab	Anti–PD-1	2	170	PFS	NCT04418648
SHR-1316	Anti–PD-1	2	60	PFS	NCT04647357
Atezolizumab (ACHILES)	Anti–PD-L1	2	212	2 year OS	NCT03540420
Ipilimumab and nivolumab (STIMULI)	Anti–CTLA-4 and anti–PD-1	2	174	OS, PFS	NCT02046733
Durvalumab plus or minus tremelimumab (ADRIATIC)	Anti–PD-L1 and anti–CTLA-4	3	724	PFS, OS	NCT03703297
Atezolizumab ± tiragolumab	Anti–PD-L1 and anti–TIGIT	2	150	PFS	NCT04308785

STIMULI Trial Results

- Randomized phase 2 trial of consolidation nivolumab/ipilimumab vs observation after chemoradiation plus PCI
- Closed prematurely due to slow accrual; Statistical plan amended to PFS as only primary endpoint
- Did not meet its primary endpoint of improving PFS with nivo/ipi consolidation
- Short period on active treatment, with a median time to nivo/ipi discontinuation of 1.7 month
- Alternative nivo/ipi dosing could be considered to reduce toxicity



Peters, et al, Annals of Oncology 2022 Jan;33(1):67-79

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Phase II/III Immunotherapy Studies in LS-SCLC: Concurrent with chemoradiation and consolidation

Agent	Mechanism of Action	Phase	Sample Size	Primary End Point	NCT
Concurrent with chemoradiation and as consolidation					
Durvalumab	Anti–PD-L1	2	51	PFS	NCT03585998
Durvalumab (DOLPHIN)	Anti–PD-L1	2	105	PFS	NCT04602533
Pembrolizumab concurrent followed by pembrolizumab ± olaparib (KEYLYNK-013)	Anti–PD-1 and PARP inhibitor	3	672	PFS, OS	NCT04624204
Atezolizumab (NRG LU-005)	Anti–PD-L1	2 or 3	506	PFS or OS	NCT03811002
Sintilimab induction plus platinum-etoposide, followed by chemoradiation and sintilimab consolidation	Anti–PD-1	2	140	PFS	NCT04189094

Key Take Home Points

- Combination chemotherapy and immunotherapy is recommended first-line treatment for extensive-stage SCLC
- Updated analysis of CASPIAN and IMpower133 show continued benefit to SCLC patients
- NCCN Guidelines® recommend lurbinectidin and topotecan in 2L setting, as well as consideration of clinical trial options
- Advances in SCLC biology will hopefully yield biomarkers to direct and personalize treatment
- Consider clinical trials for limited-stage SCLC

Yale SCLC Program

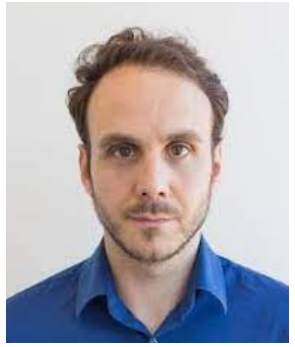
- Around 80-90 SCLC patients diagnosed annually in the Smilow Cancer Network
- Track record of robust SCLC Portfolio and accrual
  - IIT, industry, cooperative group trials
    - Ph 1 novel therapeutics, Ph 2 expansion
    - Ph 3 practice-changing trials
- SCLC clinical and tissue database
- Excellent team of clinician/scientists
  - Deep community engagement and accrual
- Biomarker ipi/nivo IIT trial (Chiang/Schalper) to study markers of IO response
- SPORE DRP grant (Chiang/Politi) to study acquired IO resistance in SCLC


Anne Chiang


Henry Park


Kurt Schalper


Katie Politi


Arnaud Augert (2022)


Anna Wurtz