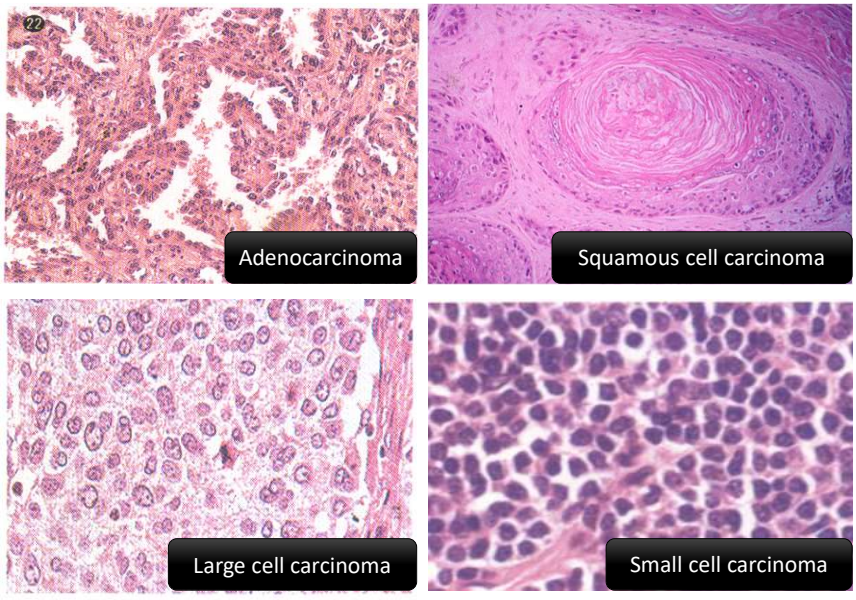
1

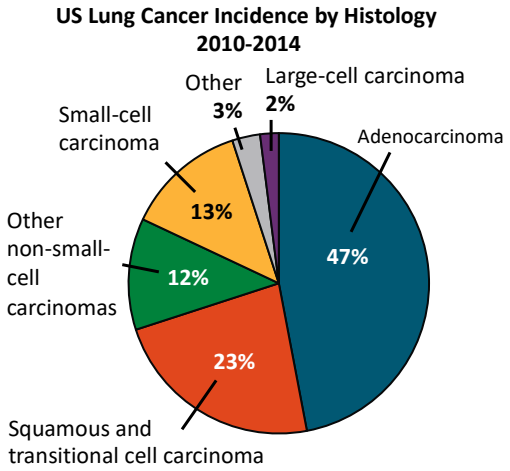
常見的肺癌組織的型態分類



2

Small-Cell Lung Cancer

- SCLC accounts for ~ 13% of all lung cancers in the US
- Previously called oat-cell carcinoma
- Associated with a history of significant tobacco use
- Unique biology: rapid proliferation, abrupt presentation, bulky central tumor, hematogenous metastases at onset
- Poor outcomes



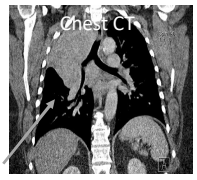
Oronsky. Neoplasia. 2017;19:842. Alvarado-Luna. Transl Lung Cancer Res. 2016;5:26. Howlander. SEER Cancer Statistics Review, 1975-2014.

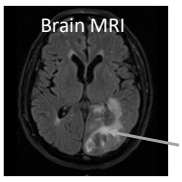
Slide credit: clinicaloptions.com

3

SCLC Clinical Presentation

- Local symptoms: cough, 50%; dyspnea, 40%; chest pain, 35%; hemoptysis, 20%; hoarseness, 10%
- Distant symptoms: weight loss, 50%; weakness, 40%; anorexia, 30%; paraneoplatic syndrome, 15%; fever, 10%
- Paraneoplastic syndromes: ectopic hormone-associated syndromes, immune-mediated neurologic syndromes





Metastatic Site, %	At Presentation	At Autopsy
Mediastinal LNs	66-80	73-87
Liver	21-27	69
Bone	27-41	54
Adrenal glands	5-31	35-65
Bone marrow	15-30	NA
Brain	10-14	28-50
Retroperitoneal LNs	3-12	29-52
Supraclavicular LNs	17	42
Pleural effusion	16-20	30
Contralateral lung	1-12	8-27
Soft tissues	5	19

Jackman. Lancet. 2005;366:1385. Images courtesy of Anna F. Farago, MD, PhD.

Slide credit: clinicaloptions.com

4

SCLC Diagnosis and Staging

- Diagnosis by FNA or biopsy
- Staging workup
  - CT chest/abdomen/pelvis
  - Brain MRI
  - PET scan to rule out distant metastases

- TNM staging system vs VA staging system

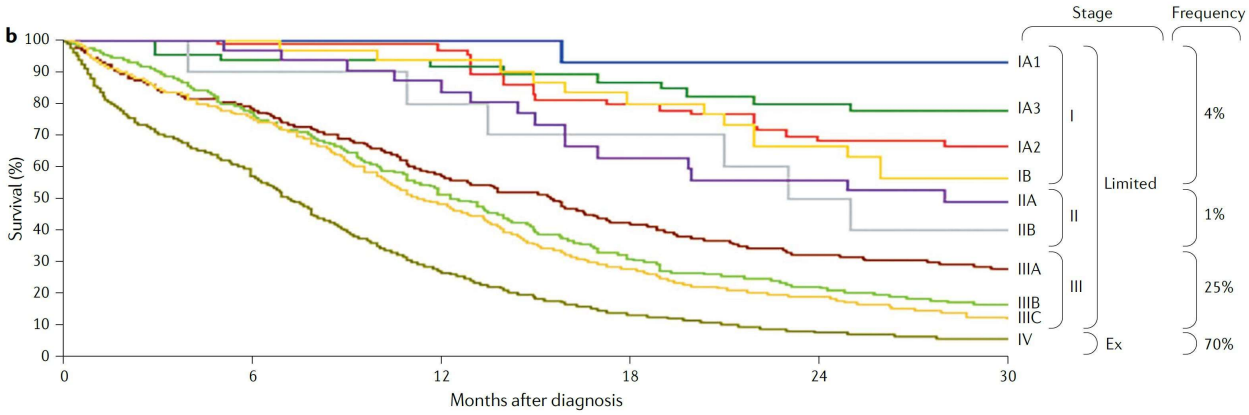
TNM Staging	VA Staging	Incidence, %
T1-T2, N0, M0 (stage I)	Limited stage	~ 5
T any, N any, M0 (stage I-III)	Limited stage; disease burden contained within radiation field	~ 30
T any, N any, M1 (stage IV)	Extensive stage; disease burden beyond radiation field	~ 65

Kalemkerian. Cancer Imaging. 2011;11:253. Alvarado-Luna. Transl Lung Cancer Res. 2016;5:26. Sabari. Nat Rev Clin Oncol. 2017;14:549

Slide credit: clinicaloptions.com

5

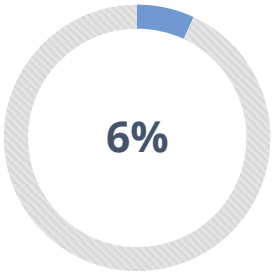
SCLC Survival Statics



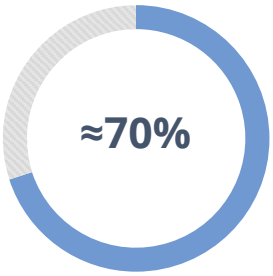
Nature Reviews Disease Primers, 2021

6

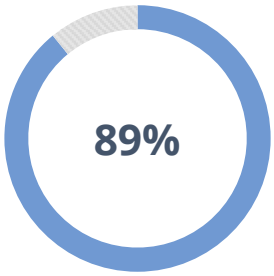
SCLC insights in Taiwan [1,2]



小細胞肺癌/肺癌
佔整體肺癌6%



Extensive stage
擴散期或稱廣泛期[2]
七成以上病人為擴散期



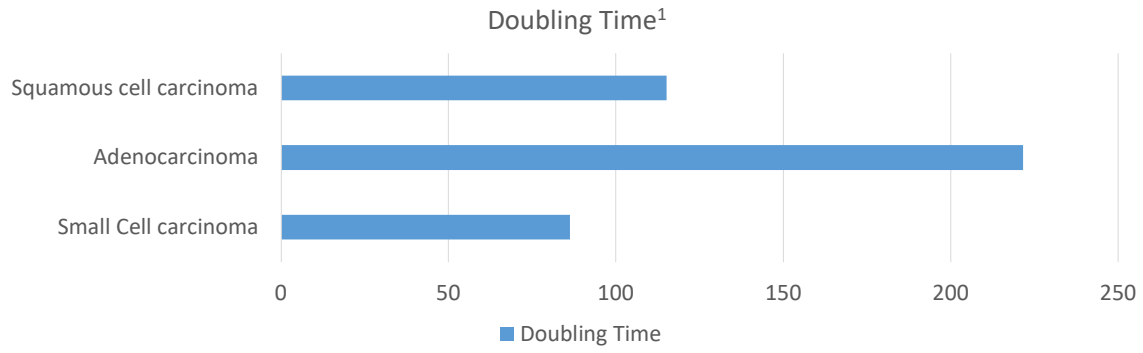
男生為主
跟吸菸有高度關係

預估每年會有600-650位ES-SCLC病人

1. 台灣癌症登記報告 107年
2. 國家衛生研究院小細胞肺癌臨床指引 https://tcog.nhri.org.tw/wp-content/uploads/2020/05/93sclc.pdf

7

Small cell doubling time



Given the neuroendocrinological origin of SCLC, it is considered the prototype of rapidly growing malignancies with doubling time in the range of 25 to 217 days according to several studies.[2]

1. Jpn J Clin Oncol. 1994 Aug;24(4):199-204
2. Harris, Kassem, et al. "Small cell lung cancer doubling time and its effect on clinical presentation: a concise review." Clinical Medicine Insights: Oncology 6 (2012): CMO-S9633.

8

Baseline characteristics of small cell lung cancer patients

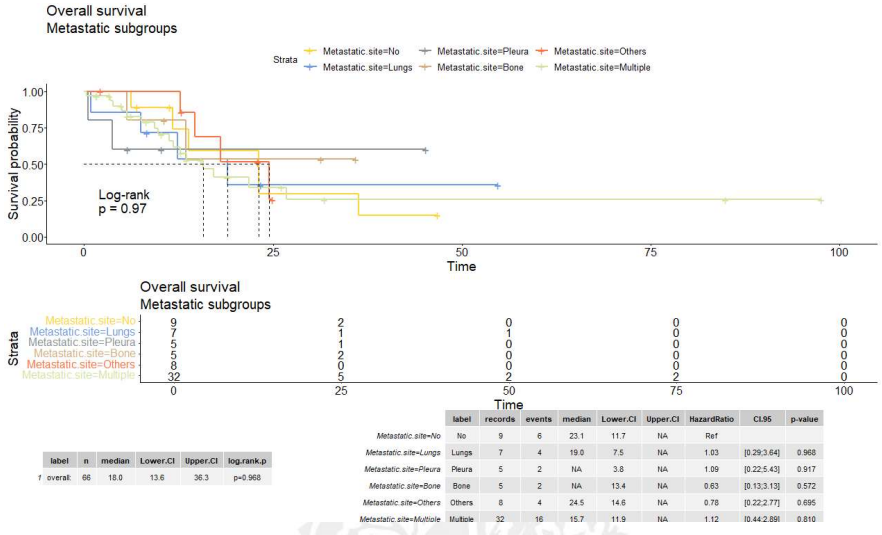
	Total		Limited stage		Extensive stage	
	N	%	N	%	N	%
Total	2707	100.00	439	16.22	2268	83.78
Age						
Median (Q1, Q3)	66 (60, 75)		67 (60, 75)		66 (59, 75)	
Gender						
Male	2446	90.36	399	90.89	2047	90.26
Female	261	9.64	40	9.11	221	9.74
Year at diagnosis						
2011	561	20.72	91	20.73	470	20.72
2012	533	19.69	84	19.13	449	19.80
2013	539	19.91	81	18.45	458	20.19
2014	510	18.84	90	20.50	420	18.52
2015	564	20.83	93	21.18	471	20.77
Operation						
Yes	146	5.39	44	10.02	102	4.50
No	2561	94.61	395	89.98	2166	95.50
Radiation therapy						
Yes	1385	51.16	275	62.64	1110	48.94
No	1322	48.84	164	37.36	1158	51.06
ECOG PS						
0-1	1856	68.56	354	80.64	1502	66.23
≧2	600	22.16	47	10.71	553	24.38
Unknown	251	9.27	38	8.66	213	9.39
Accreditation level of hospital						
Medical Center	863	31.88	152	34.62	711	31.35
Regional Hospital	423	15.63	75	17.08	348	15.34
District Hospital	1421	52.49	212	48.29	1209	53.31

Median OS in LS: 16.92 months, 2 yr OS: 33.5%

Median OS in ES: 8.71 months, 2 yr OS: 10.8%

Chiang et al. JCMA 2021

9



label	n	median	Lower.CI	Upper.CI	log.rank.p
1 overall	66	18.0	13.6	36.3	p=0.968

label	records	events	median	Lower.CI	Upper.CI	HazardRatio	CI.95	p-value
Metastatic.site=No	No	9	6	23.1	11.7	NA	Ref	
Metastatic.site=Lungs	Lungs	7	4	19.0	7.5	NA	1.03	[0.29;3.64]	0.968
Metastatic.site=Pleura	Pleura	5	2	NA	3.8	NA	1.09	[0.22;5.43]	0.917
Metastatic.site=Bone	Bone	5	2	NA	13.4	NA	0.63	[0.13;3.13]	0.572
Metastatic.site=Others	Others	8	4	24.5	14.6	NA	0.78	[0.22;2.77]	0.695
Metastatic.site=Multiple	Multiple	32	16	15.7	11.9	NA	1.12	[0.44;2.89]	0.810

Table 4: Study outcomes among treated patients	
	Overall (N=70)
Overall survival (OS; months)	
Median survival (95% CI)	18.03 (13.57, 36.33)

10

SCLC, factoids

- 15 – 25 % of all lung cancers
- Almost exclusively in smokers
- Distinguished from NSCLC by:
  - Rapid doubling time
  - High growth fraction
  - Early development of wide-spread mets
- Considered highly responsive to “chems and beams”
- BUT…usually relapses within 2 years despite treatment
- Overall, only 3 –8 % of all patients survive more than 5 years
- Most common malignancy associated with Neurologic paraneoplastic syndromes

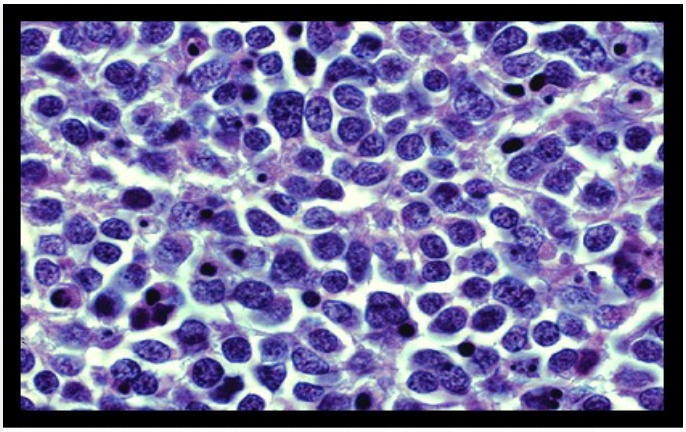
11

SCLC, pathology

- Most recent (1999) WHO classification
  - Classical small cell carcinoma
  - Large cell neuroendocrine cancer
  - Combined small cell carcinoma with some NSCLC
- Cells are approx. 2 X’s the size of normal lymphocytes

12

SCLC, pathology



Small cell carcinoma of the lung High magnification photomicrograph showing the typical cytological features of small cell carcinoma of the lung. Courtesy of Jeffrey Myers, MD.

13

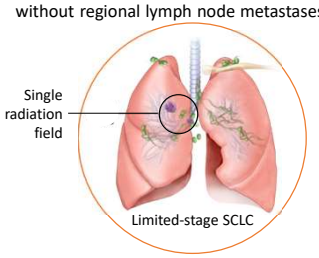
The Treatment of ES-SCLC in Combination with Chemotherapy

14

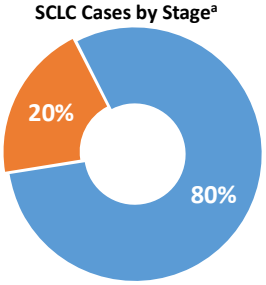
Most Cases of SCLC Are Diagnosed in Advanced Stages, Contributing to a Poor Prognosis[1,2]

SCLC accounts for ≈13% of all lung cancer cases and is most commonly staged using the 2-stage VALSG system[1,3,4]

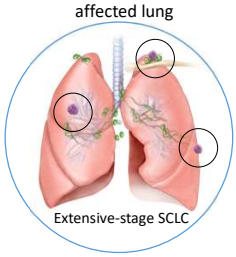
Limited stage[5,6]:
Disease confined to a single radiation port (typically confined to 1 hemithorax with or without regional lymph node metastases)



SCLC Cases by Stage[a]



Extensive stage[6]:
Disease that has spread to tissue outside of the originally affected lung



Furthermore, ≈10% of patients with ES-SCLC present with asymptomatic brain metastases, further contributing to a poor prognosis.[7-10]

[a]Data from Kantar Health Database, United States, 2018.

ES-SCLC, extensive-stage small cell lung cancer; SCLC, small cell lung cancer; VALSG, Veterans Administration Lung Study Group.

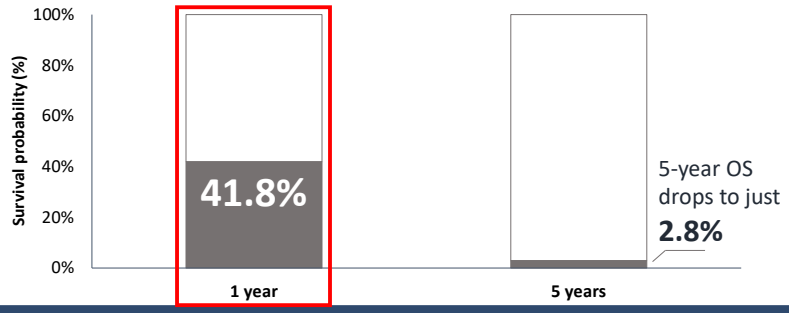
1. Farago AF, et al. *Transl Lung Cancer Res*. 2018;7(1):69-79. 2. Petrovic M, et al. *Med Oncol*. 2014;31(2):823. 3. Kantar Health Database. SCLC epidemiology. 2018. 4. Howlader N, et al, eds. SEER cancer statistics review (CSR) 1975-2016. Published April 2019. Accessed January 15, 2020. 5. Sabari JK, et al. *Nat Rev Clin Oncol*. 2017;14(9):549-561. 6. Stahel RA, et al. *Lung Cancer*. 1989;5:119-126. 7. Wang S, et al. *Mayo Clin Proc*. 2019;94(8):1599-1622. 8. Slotman B, et al. *N Engl J Med*. 2007;357(7):664-672. 9. Brueckl WM, et al. *Anticancer Res*. 2006;26(6C):4825-4832. 10. Seute T, et al. *J Clin Oncol*. 2006;24(13):2079-2083.

15

Typically, Patients With ES-SCLC Live Less Than 1 Year After Diagnosis[1,2]

Historically, median OS has been about 8-10 months for patients receiving 1L treatment for ES-SCLC.[2,3]

OVERALL SURVIVAL IN ES-SCLC (n=313)[2,a]



ES-SCLC needs 1L therapies that can extend survival for more patients.[4]

[a]These data are based on an analysis of 1,032 patients with SCLC (extensive stage, limited stage, or not classifiable) from the H. Lee Moffitt Cancer Center and Research Institute. Log-rank statistics were used to assess survival rates across 2 time periods: 1986 to 1999 (n=410) and 2000 to 2008 (n=622). Data presented here are for the ES-SCLC cohort (n=313), during the 2000-2008 time period.[3]

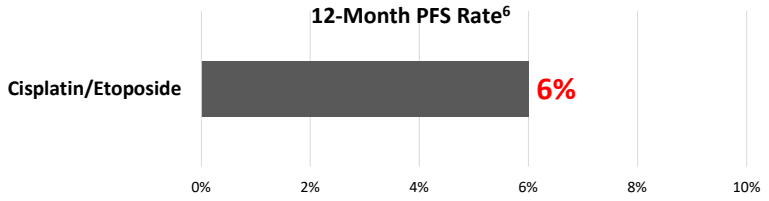
1L, first line; ES-SCLC, extensive-stage small cell lung cancer; OS, overall survival.

1. Foster NR, et al. *J Thorac Oncol*. 2015;10(7):1099-1106. 2. Schabath MB, et al. *Lung Cancer*. 2014;86(1):14-21. 3. Farago AF, et al. *Transl Lung Cancer Res*. 2018;7(1):69-79. 4. Rudin CM, et al. *J Clin Oncol*. 2015;33(34):4106-4111.

16

Improving Durability of Response to Treatment Remains Critical in ES-SCLC[1-5]

PFS has historically been ≈6% at 12 months with etoposide + platinum-based chemotherapy.[6,a]



Almost all patients experience rapid relapse[2,4,5]

- Despite an initial sensitivity to chemotherapy, patients with ES-SCLC relapse within months

Durability of response to 1L chemotherapy strongly predicts overall survival in ES-SCLC.[4,7-9]

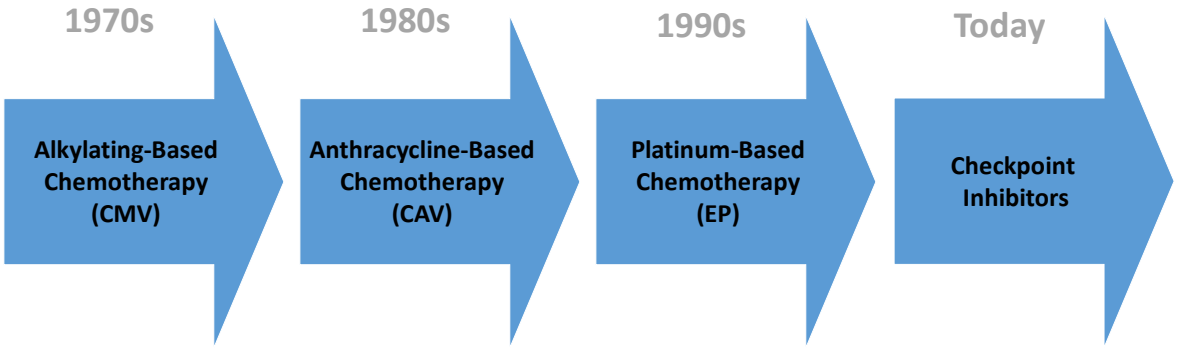
[a]Based on one study with 327 patients treated with EP from 2002 to 2007.[6]

1L, first line; ES-SCLC, extensive-stage small cell lung cancer; PFS, progression-free survival.

1. Rudin CM, et al. *J Clin Oncol*. 2015;33(34):4106-4111. 2. Farago AF, et al. *Transl Lung Cancer Res*. 2018;7(1):69-79. 3. Rossi A, et al. *J Clin Oncol*. 2012;30(14):1692-1698. 4. Pietanza MC, et al. *Clin Cancer Res*. 2015;21(10):2244-2255. 5. Sabari JK, et al. *Nat Rev Clin Oncol*. 2017;14(9):549-561. 6. Lara PN Jr, et al. *J Clin Oncol*. 2009;27(15):2530-2535. 7. Fukui T, et al. *BMC Cancer*. 2016;16:197. 8. Owonikoko TK, et al. *J Thorac Oncol*. 2012;7(5):866-872. 9. Rocha-Lima CM, et al. *Ann Oncol*. 2007;18(2):331-337.

17

Evolution of Systemic Therapy in Small-Cell Lung Cancer



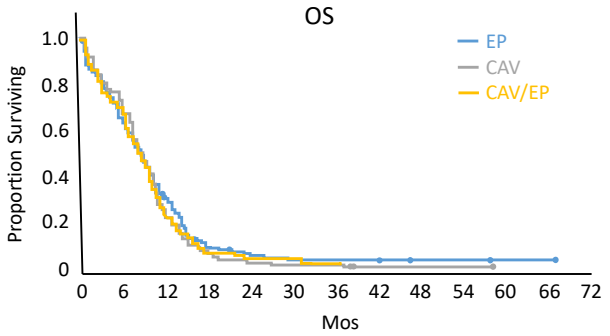
Sabari. Nat Rev Clin Oncol. 2017;14:549. Saleh. Immunotherapy. 2019;11:457.

Slide credit: clinicaloptions.com

18

Historic Standard of Care for ES-SCLC: Platinum + Etoposide Chemotherapy

- Phase III study of EP vs CAV vs CAV alternating with EP (N = 437)
  - Initially responsive to EP, often rapid and dramatic
    - ORR: 61% (CR: 10%)
  - However, responses to EP are transient
    - Median PFS: 4.3 mos
    - Median OS: 8.6 mos

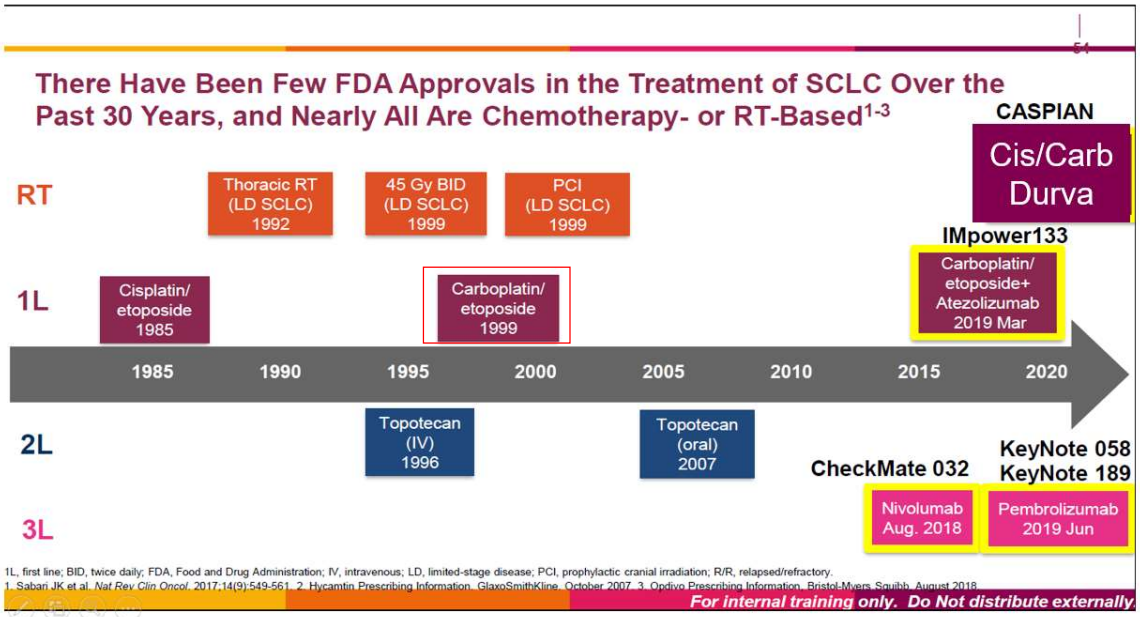


Roth. J Clin Oncol. 1992;10:282.

Slide credit: clinicaloptions.com

19

SCLC的藥物治療演進



20

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2022
Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY

PRIMARY OR ADJUVANT THERAPY FOR LIMITED-STAGE SCLC:

Four cycles of systemic therapy are recommended.
Planned cycle length should be every 21–28 days during concurrent RT.
During systemic therapy + RT, cisplatin/etoposide is recommended (category 1).
The use of myeloid growth factors is not recommended during concurrent systemic therapy plus RT (category 1 for not using GM-CSF).[1]

Preferred Regimens
- Cisplatin 75 mg/m² day 1 and etoposide 100 mg/m² days 1, 2, 3[2]
- Cisplatin 60 mg/m² day 1 and etoposide 120 mg/m² days 1, 2, 3[3]

Other Recommended Regimens
- Cisplatin 25 mg/m² days 1, 2, 3 and etoposide 100 mg/m² days 1, 2, 3[2]
- Carboplatin AUC 5–6 day 1 and etoposide 100 mg/m² days 1, 2, 3[a,4]

PRIMARY THERAPY FOR EXTENSIVE-STAGE SCLC:

Four cycles of therapy are recommended, but some patients may receive up to 6 cycles based on response and tolerability after 4 cycles.

Preferred Regimens
- Carboplatin AUC 5 day 1 and etoposide 100 mg/m² days 1, 2, 3 and atezolizumab 1,200 mg day 1 every 21 days x 4 cycles followed by maintenance atezolizumab 1,200 mg day 1, every 21 days (category 1 for all)[b,5]
- Carboplatin AUC 5 day 1 and etoposide 100 mg/m² days 1, 2, 3 and atezolizumab 1,200 mg day 1 every 21 days x 4 cycles followed by maintenance atezolizumab 1,680 mg day 1, every 28 days[b]
- Carboplatin AUC 5–6 day 1 and etoposide 80–100 mg/m² days 1, 2, 3 and durvalumab 1,500 mg day 1 every 21 days x 4 cycles followed by maintenance durvalumab 1,500 mg day 1 every 28 days (category 1 for all)[b,6]
- Cisplatin 75–80 mg/m² day 1 and etoposide 80–100 mg/m² days 1, 2, 3 and durvalumab 1,500 mg day 1 every 21 days x 4 cycles followed by maintenance durvalumab 1,500 mg day 1 every 28 days (category 1 for all)[b,6]

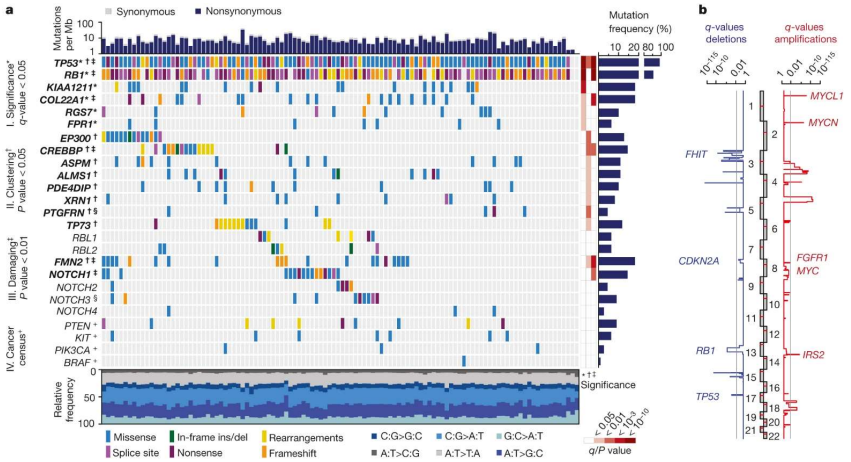
Other Recommended Regimens
- Carboplatin AUC 5–6 day 1 and etoposide 100 mg/m² days 1, 2, 3[7]
- Cisplatin 75 mg/m² day 1 and etoposide 100 mg/m² days 1, 2, 3[8]
- Cisplatin 80 mg/m² day 1 and etoposide 80 mg/m² days 1, 2, 3[9]
- Cisplatin 25 mg/m² days 1, 2, 3 and etoposide 100 mg/m² days 1, 2, 3[10]

Useful In Certain Circumstances
- Carboplatin AUC 5 day 1 and irinotecan 50 mg/m² days 1, 8, 15[11]
- Cisplatin 60 mg/m² day 1 and irinotecan 60 mg/m² days 1, 8, 15[12]
- Cisplatin 30 mg/m² days 1, 8 and irinotecan 65 mg/m² days 1, 8[13]

Subsequent Systemic Therapy (SCL-E 2 of 5)
Response Assessment (SCL-E 3 of 5)
References (SCL-E 4 of 5)

21

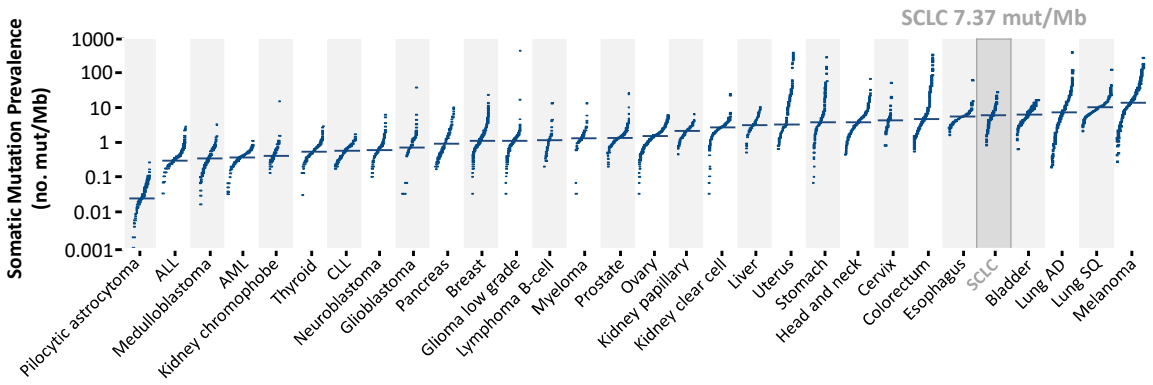
Why Has Progress Been Slow? Absence of Driver Mutations in SCLC



Slide credit: clinicaloptions.com

22

SCLC Has a High Tumor Mutational Burden



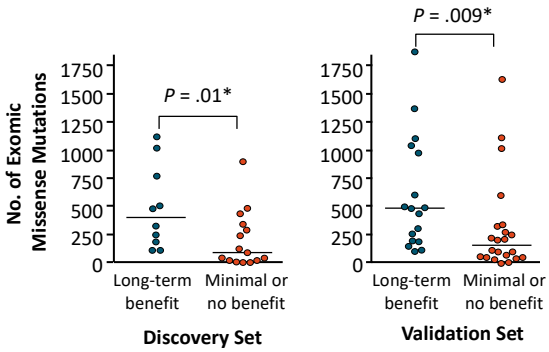
Peifer. Nat Genet. 2012;44:1104. Alexandrov. Nature. 2013;500:415.

Slide credit: clinicaloptions.com

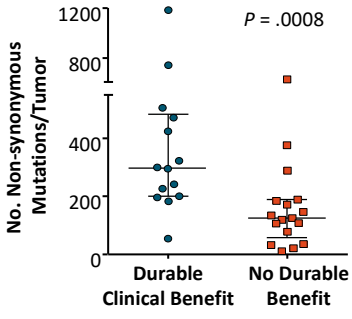
23

Mutational Burden Is Associated With Improved Efficacy of Immune Checkpoint Inhibitors

- Mutational burden in melanoma patients treated with ipilimumab or tremelimumab with long-term vs minimal or no benefit[1]



- Mutation burden in NSCLC patients treated with pembrolizumab with durable clinical benefit compared to those without durable benefit[2]

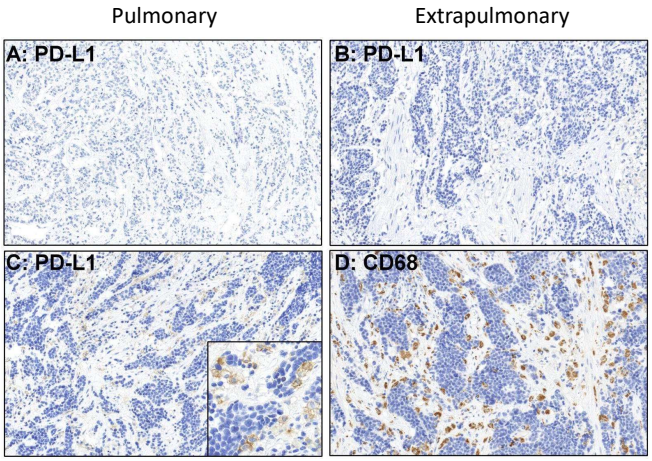


1. Snyder. NEJM. 2014;371:2189. 2. Rizvi. Science. 2015;348:124.

Slide credit: clinicaloptions.com

24

PD-L1 Expression in SCLC



- No PD-L1 expression detected by IHC on tumor cells in 94 SCLC cases
- 18.5% of cases (17/92) showed PD-L1 expression in tumor-infiltrating macrophages
- 48% (45/94) of cases showed PD-1–positive T-lymphocytes

Schultheis. Eur J Cancer. 2015;51:421.

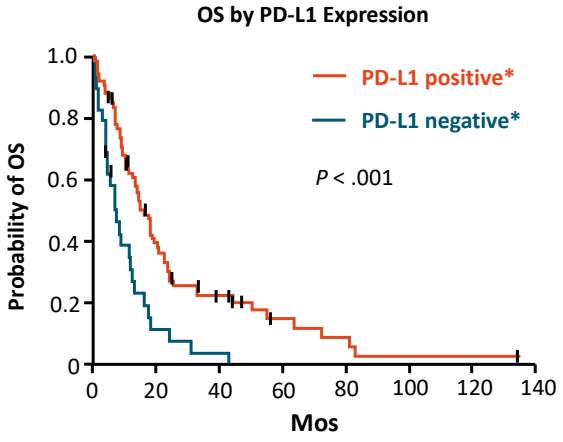
Slide credit: clinicaloptions.com

25

Association of PD-L1 Expression in SCLC With Survival

- PD-L1 expression was observed in 72% (73/102) of SCLC specimens
  - Significantly correlated with limited disease stage
  - Independently predictive of favorable outcome

Factor for OS in Multivariate Analysis	HR	95% CI	*P* Value
PS (0-1/2-3)	0.390	0.192-0.841	.018
Stage (LS/ES)	0.403	0.199-0.804	.010
NSE level (low/high)	0.671	0.358-1.225	.196
LDH level (normal/abnormal)	1.130	0.628-1.995	.679
PD-L1 expression (positive/negative)	0.435	0.241-0.803	.008



*PD-L1 positivity: ≥ 5% of cells; PD-L1 negativity: < 5% of cells.

Ishii. J Thorac Oncol. 2015;10:426.

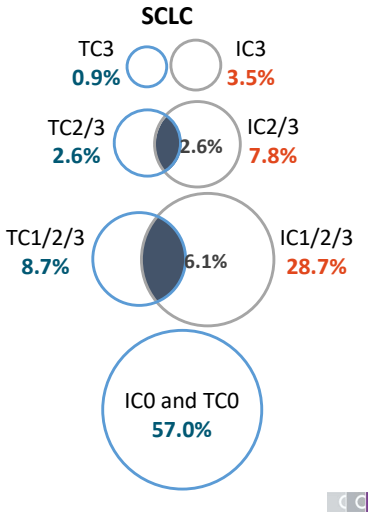
Slide credit: clinicaloptions.com

26

PD-L1 Prevalence Is Lower in SCLC Than NSCLC

PD-L1–Selected Population	NSCLC	SCLC*
	PCD4989g, FIR, POPLAR (n = 1360)	PCD4989g† (n = 115)
TC3 or IC3	~ 15.0%	~ 4.3%
TC2/3 or IC2/3	~ 38.0%	~ 13.0%
TC1/2/3 or IC1/2/3	~ 70.0%	~ 43.5%
TC0 and IC0	~ 30.0%	~ 56.5%

*Prevalence based on biopsy/resections may not reflect true first-line SCLC population (eg, high % FNAs).
†PCD4989g enrollment initially low due to strict PD-L1 selection criteria with cutoff of IC2/3 (n = 5). Also concerns over SCLC tissue evaluability (eg, crush artifact, higher FNA rate, lower tissue availability compared to NSCLC) and timeliness of prospective biomarker evaluation due to SCLC clinical characteristics (fast clinical deterioration and need for rapid treatment initiation).

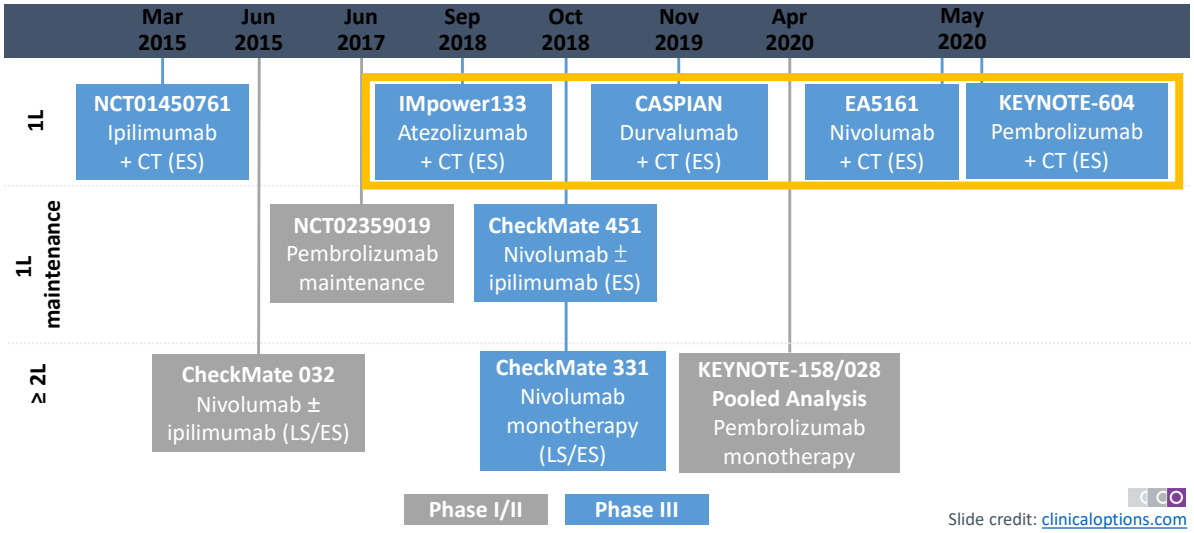


Sequist. ESMO 2016. Abstr 1425PD.

Slide credit: clinicaloptions.com

27

Overview of Key Studies of Immune Checkpoint Inhibitors in SCLC



Slide credit: clinicaloptions.com

28

Rationale to Combine ICI With Chemotherapy in SCLC

Chemotherapy

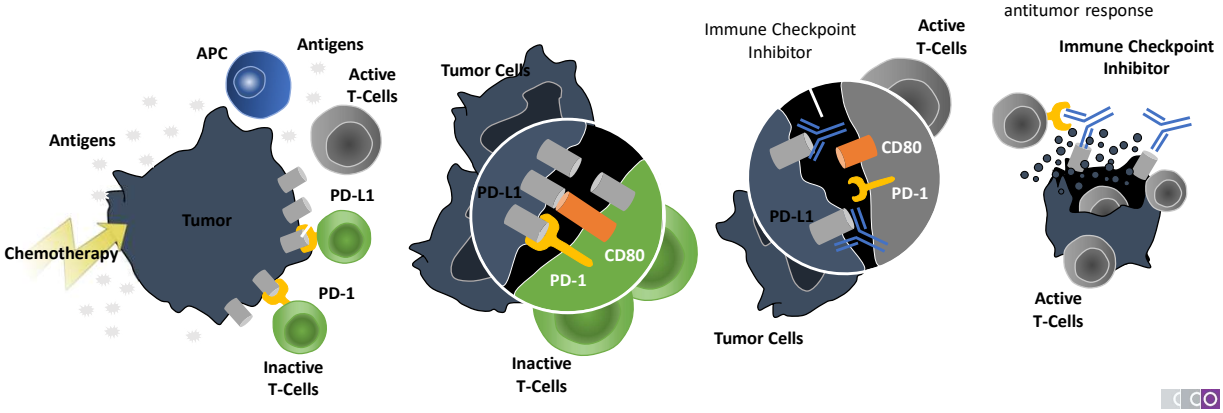
1. Chemotherapy-induced tumor cell killing may induce tumor antigen release and exposure to immune system

2. PD-L1 overexpression leads to immune cell invasion and T-cell inhibition

PD-1/PD-L1 Inhibition

3. PD-1/PD-L1 inhibition restores tumor-specific T-cell immunity

4. Reversal of immune suppression leads to deeper, more durable systemic antitumor response



Wargo. Semin Oncol. 2015;42:601. Shafique. Expert Opin Biol Ther. 2019;19:225.

Slide credit: clinicaloptions.com

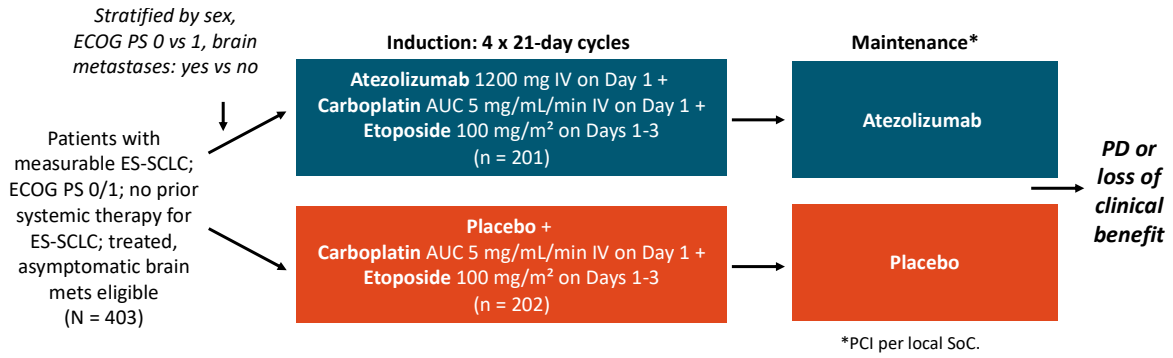
29

Impower 133 in 1stL ES-SCLC

30

IMpower133: Atezolizumab + Chemotherapy for Advanced SCLC

- Double-blind, randomized, placebo-controlled phase I/III trial

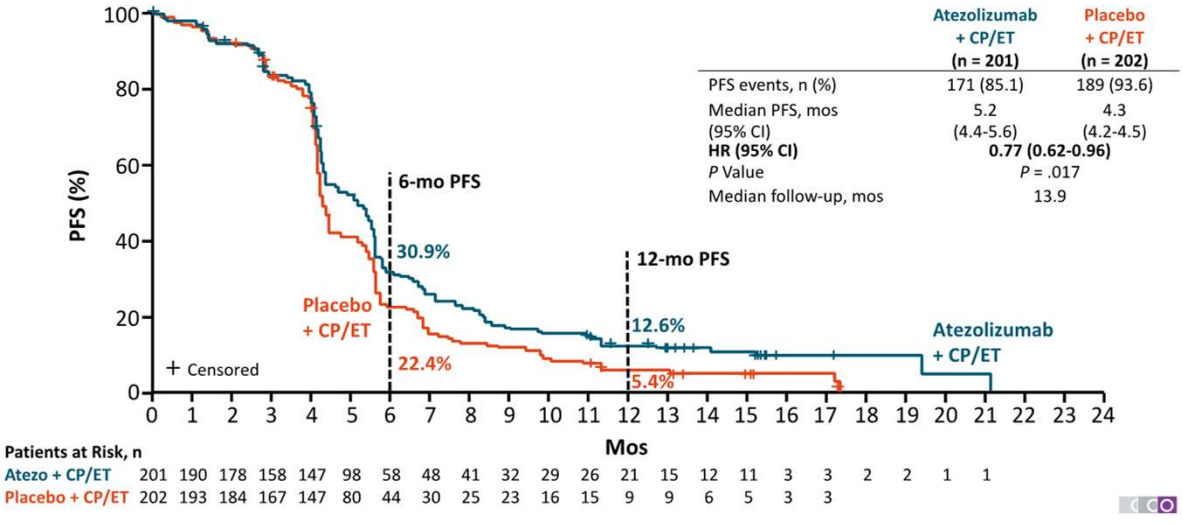


- Coprimary endpoints: OS, PFS by investigator assessment
- Secondary endpoints: ORR, DoR, safety

Liu. IASLC WCLC. 2018. Abstr PL0-207. Horn. NEJM. 2018;379:2220.

31

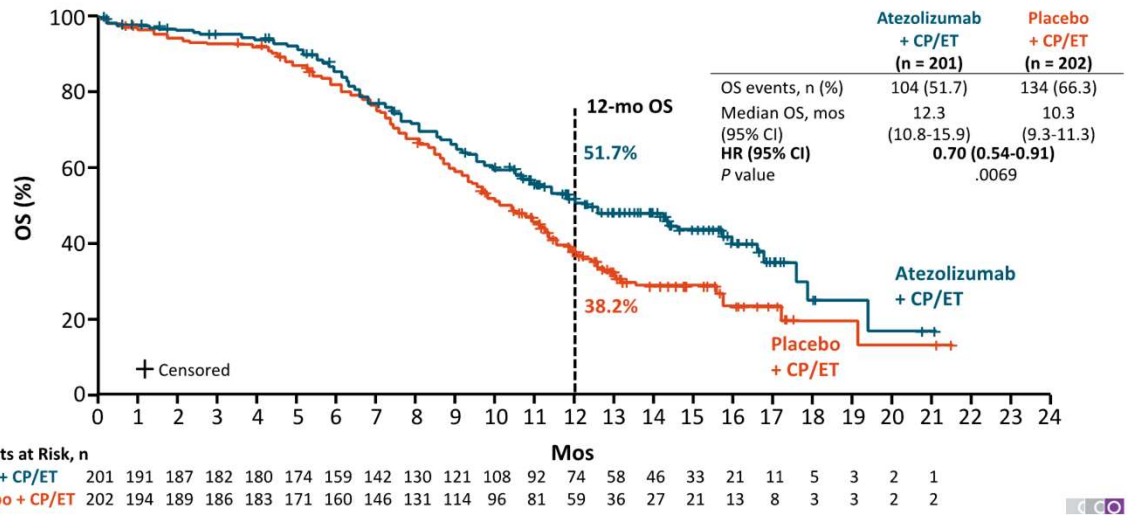
IMpower133: PFS (Coprimary Endpoint)



	Atezolizumab + CP/ET (n = 201)	Placebo + CP/ET (n = 202)
PFS events, n (%)	171 (85.1)	189 (93.6)
Median PFS, mos (95% CI)	5.2 (4.4-5.6)	4.3 (4.2-4.5)
HR (95% CI)	**0.77 (0.62-0.96)**	
P Value	*P* = .017	
Median follow-up, mos	13.9	

32

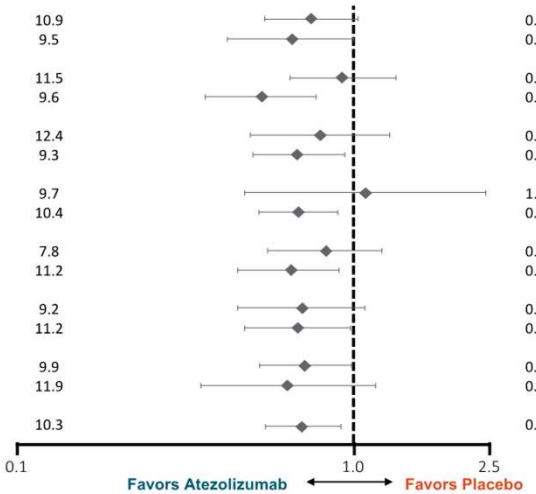
IMpower133: OS (Coprimary Endpoint)



33

IMpower133: OS by Subgroup

Subgroup	Median OS, Mos: Atezolizumab + CP/ET	Median OS, Mos: Placebo + CP/ET	HR (95% CI)
Male (n = 261)	12.3	10.9	0.74 (0.54-1.02)
Female (n = 142)	12.5	9.5	0.65 (0.42-1.00)
< 65 yrs (n = 217)	12.1	11.5	0.92 (0.64-1.32)
≥ 65 yrs (n = 186)	12.5	9.6	0.53 (0.36-0.77)
ECOG PS 0 (n = 140)	16.6	12.4	0.79 (0.49-1.27)
ECOG PS 1 (n = 263)	11.4	9.3	0.68 (0.50-0.93)
Brain metastases (n = 35)	8.5	9.7	1.07 (0.47-2.43)
No brain metastases (n = 368)	12.6	10.4	0.68 (0.52-0.89)
Liver metastases (n = 149)	9.3	7.8	0.81 (0.55-1.20)
No liver metastases (n = 254)	16.8	11.2	0.64 (0.45-0.90)
bTMB < 10 mut/Mb (n = 139)	11.8	9.2	0.70 (0.45-1.07)
bTMB ≥ 10 mut/Mb (n = 212)	14.6	11.2	0.68 (0.47-0.97)
bTMB < 16 mut/Mb (n = 271)	12.5	9.9	0.71 (0.52-0.98)
bTMB ≥ 16 mut/Mb (n = 80)	17.8	11.9	0.63 (0.35-1.15)
ITT (N = 403)	12.3	10.3	0.70 (0.54-0.91)



34

IMpower133: Adverse Events

Events, n (%)	Atezolizumab + CP/ET (n = 198)	Placebo + CP/ET (n = 196)
≥ 1 AE	198 (100)	189 (96.4)
Grade 3/4 AEs	133 (67.2)	125 (63.8)
Treatment-related AEs	188 (94.9)	181 (92.3)
Serious AEs	74 (37.4)	68 (34.7)
Immune-related AEs	79 (39.9)	48 (24.5)
AEs leading to withdrawal from any study medication	22 (11.1)	6 (3.1)
▪ Atezolizumab or placebo	21 (10.6)	5 (2.6)
▪ Carboplatin	5 (2.5)	1 (0.5)
▪ Etoposide	8 (4.0)	2 (1.0)
Treatment-related deaths	3 (1.5)	3 (1.5)

- Median duration of treatment with atezolizumab: 4.7 mos (range: 0-21)
- Median no. of doses received: atezolizumab, 7 (range: 1-30); carboplatin, 4; etoposide, 12 (chemotherapy doses the same for both treatment groups)

Horn. NEJM. 2018;379:2220. Liu. IASLC WCLC 2018. Abstr PL0-207.

Slide credit: clinicaloptions.com

35

VIRTUAL 2020 ESMO congress

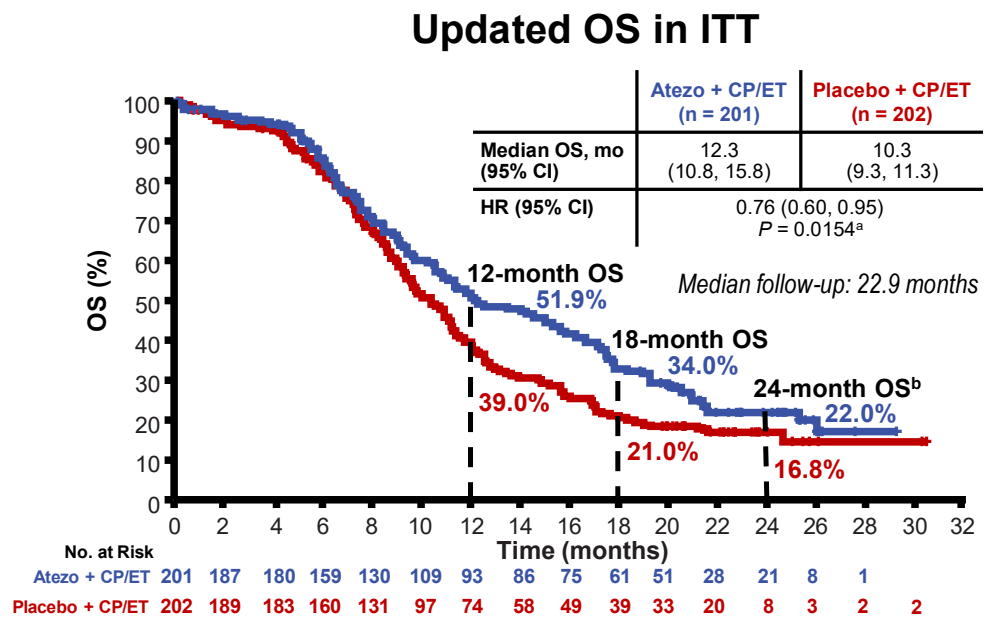
IMpower133: characterisation of long-term survivors treated with first line chemotherapy ± atezolizumab in extensive-stage small cell lung cancer

Stephen V. Liu,[1] Leora Horn,[2] Tony S. K. Mok,[3] Aaron S. Mansfield,[4] Richard De Boer,[5] Gyorgy Losonczy,[6] Shunichi Sugawara,[7] Rafal Dziadziuszko,[8] Maciej Krzakowski,[9] Alexey Smolin,[10] Maximilian Hochmair,[11] Marina Garassino,[12] Sivuonthanh Lam,[13] Mark McCleland,[13] Andres Cardona,[14] Stefanie Morris,[14] Martin Reck[15]

[1]Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC, USA; [2]Vanderbilt University Medical Center, Nashville, TN, USA; [3]State Key Laboratory of Translational Oncology, The Chinese University of Hong Kong, Hong Kong; [4]Division of Medical Oncology, Mayo Clinic, Rochester, MN, USA; [5]Peter MacCallum Cancer Centre, Melbourne, Australia; [6]Department of Pulmonology, Semmelweis University, Budapest, Hungary; [7]Sendai Kousei Hospital, Sendai, Japan; [8]Medical University of Gdańsk, Gdańsk, Poland; [9]Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [10]Department of Radiology, Burdenko Main Military Clinical Hospital, Moscow, Russia; [11]Department of Respiratory & Critical Care Medicine, Karl Landsteiner Institute of Lung Research & Pulmonary Oncology, Krankenhaus Nord, Vienna, Austria; [12]Thoracic Oncology Unit, Division of Medical Oncology, Foundation IRCCS-Italian National Cancer Institute, Milan, Italy; [13]Genentech, Inc., South San Francisco, CA, USA; [14]F. Hoffmann-La Roche, Ltd, Basel, Switzerland; [15]Lungen Clinic, Airway Research Center North, German Center for Lung Research, Grosshansdorf, Germany

36

IMpower133: OS (Coprimary Endpoint)



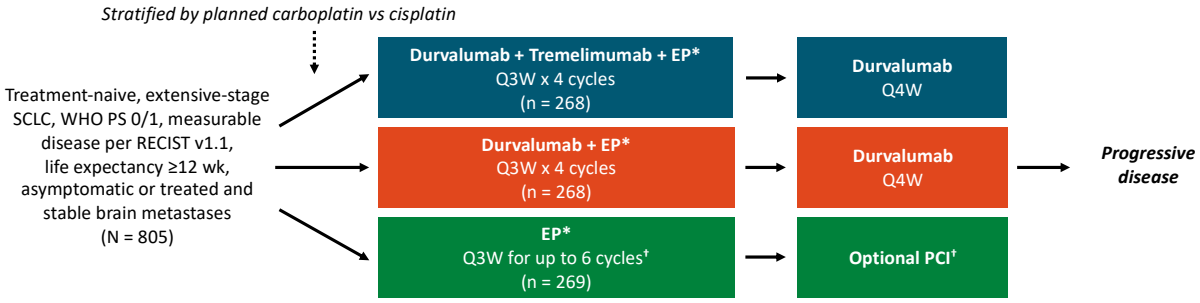
37

Caspian Study in 1stL ES-SCLC

38

CASPIAN 3-Yr Update: Study Design

- Randomized, open-label, multicenter phase III study



*Etoposide 80-100 mg/m² with either carboplatin AUC 5-6 or cisplatin 75-80 mg/m², durvalumab 1500 mg, tremelimumab 75 mg.
†Per investigator discretion, additional 2 cycles of EP (6 cycles total) and PCI.

- **Primary endpoint:** OS
- **Secondary endpoints:** PFS and ORR (not collected since last data cutoff), safety (limited to serious AEs, including death)

Paz-Ares. ESMO 2021. Abstr LBA61.

Slide credit: clinicaloptions.com

39

CASPIAN study

mOS **13個月**
30年重大突破

Quality of Life updated

OS24 **22.2%,**
mOS 12.9個月

PFS12 **17.9%,**
為EP組3倍

OS36 **17.6%**
唯一三年

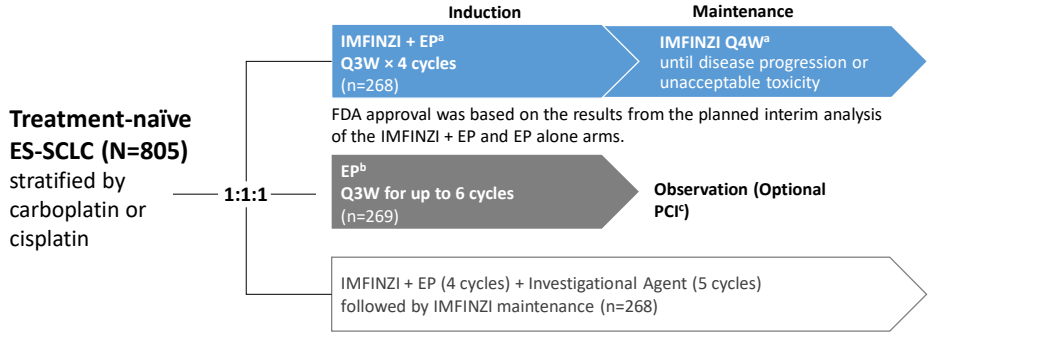
40

*Tremelizumab is not indicated in Taiwan

40

IMFINZI® (durvalumab) Approval in ES-SCLC Is Based on the Phase 3 CASPIAN Study[1]

Large, randomized, open-label multicenter study of IMFINZI + EP vs EP alone[1,2]



Primary endpoint[1,2]	Key secondary endpoints[1,2]	
OS	• PFS[d] • ORR (unconfirmed)[d] • OS at 18 months	• PFS at 6 and 12 months • HRQoL patient-reported outcomes

[a]IMFINZI 1500 mg + either carboplatin (AUC 5 mg/mL/min or 6 mg/mL/min) or cisplatin (75 mg/m²-80 mg/m²) on Day 1 and etoposide (80 mg/m²-100 mg/m²) intravenously on Days 1, 2, and 3 of each 21-day cycle for a maximum of 4 cycles, followed by IMFINZI 1500 mg every 4 weeks until disease progression or unacceptable toxicity. [b]Either carboplatin (AUC 5 mg/mL/min or 6 mg/mL/min) or cisplatin (75 mg/m²-80 mg/m²) on Day 1 and etoposide (80 mg/m²-100 mg/m²) intravenously on Days 1, 2, and 3 of each 21-day cycle for 4 to 6 cycles. [c]8% of patients who were treated with EP alone received PCI post-EP. [d]Assessed using investigator assessments according to RECIST v1.1.
EP, etoposide/platinum-based chemotherapy; ES-SCLC, extensive-stage small cell lung cancer; FDA, US Food and Drug Administration; HRQoL, health-related quality of life; ORR, objective response rate; OS, overall survival; PCI, prophylactic cranial irradiation; PFS, progression-free survival; Q3W, every 3 weeks; Q4W, every 4 weeks.
1. IMFINZI® (durvalumab) [Prescribing Information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2020. 2. Paz-Ares L, et al. *Lancet*. 2019;394(10212):1929-1939.

41

The CASPIAN Study Compared IMFINZI + EP Against Real-World Treatment With EP in ES-SCLC[1,2]

CASPIAN allowed for[1]:

Investigator's choice of platinum-based chemotherapy[a]

Patients with asymptomatic or treated brain metastases[b]

The control arm allowed for[3]:

Up to 6 cycles of chemotherapy

PCI per investigator's discretion

[a]78% received carboplatin and 25% received cisplatin in the IMFINZI + EP arm; 78% received carboplatin and 25% received cisplatin in the EP alone arm. [b]Patients with confirmed brain metastases had to be treated and stable off steroids and anticonvulsants for at least 1 month prior to study treatment. Patients with suspected brain metastases at screening should have a CT/MRI of the brain prior to study entry.

EP, etoposide/platinum-based chemotherapy; ES-SCLC, extensive-stage small cell lung cancer; PCI, prophylactic cranial irradiation.

1. Paz-Ares L, et al. *Lancet*. 2019;394(10212):1929-1939. 2. Rudin CM, et al. *J Clin Oncol*. 2015;33(34):4106-4111. 3. IMFINZI® (durvalumab) [Prescribing Information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2020.

42

Baseline Patient Characteristics Were Well Balanced Between the IMFINZI + EP and EP Arms

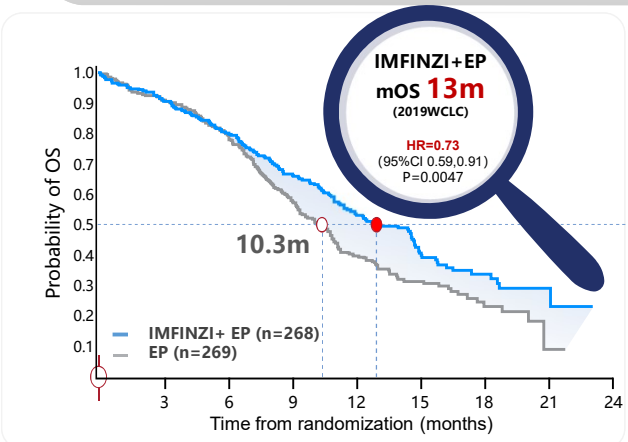
Patient Characteristics	IMFINZI + EP (n=268)	EP alone (n=269)
Median age (range) (years)	62 (58-68)	63 (57-68)
Gender		
Male	71%	68%
Female	29%	32%
ECOG/WHO PS		
0	37%	33%
1	63%	67%
Stage		
III	10%	9%
IV	90%	91%
Smoking history		
Current smoker/former smoker	92%	94%
Never smoker	8%	6%
Brain or CNS metastases	10%	10%
Liver metastases	40%	39%

PD-L1 testing was not required.

CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; EP, etoposide/platinum-based chemotherapy; PD-L1, programmed death-ligand 1; PS, performance status; WHO, World Health Organization.
Paz-Ares L, et al. *Lancet*. 2019;394(10212):1929-1939.

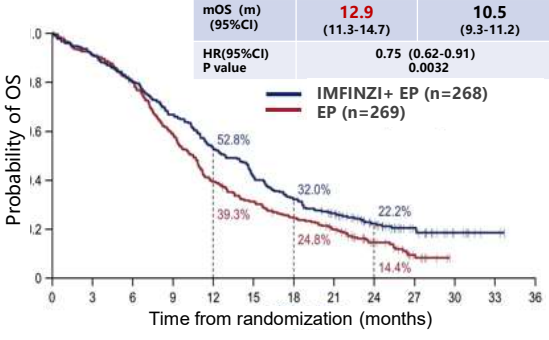
43

Half of Patients Were Still Alive at 13 Months With IMFINZI + EP



IMFINZI+EP mOS 12.9m (2020 ASCO updated)

	IMFINZI+EP (n=268)	EP (n=269)
mOS (m) (95%CI)	12.9 (11.3-14.7)	10.5 (9.3-11.2)
HR(95%CI) P value	0.75 (0.62-0.91) 0.0032	

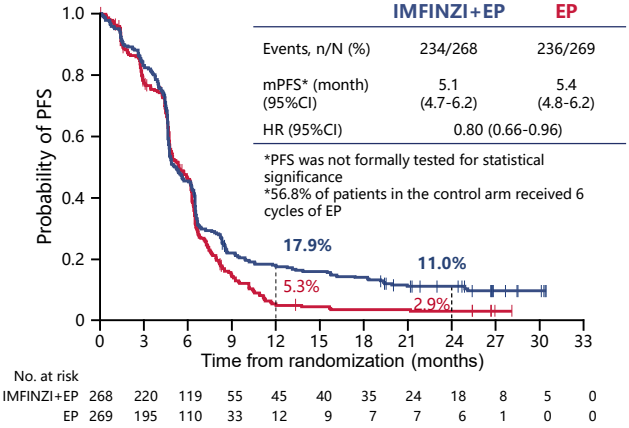


Transform months into the potential for years in ES-SCLC

44 Paz-Ares L, et al. Lancet. 2019;394(10212):1929-1939.
Paz-Ares L, et al. 2020 ASCO. Abstract 9002.

44

CASPIAN：IMFINZI+EP 1Y PFS rate increased by 3 times



PFS benefit

	IMFINZI+EP	EP
Events, n/N (%)	234/268	236/269
mPFS* (month) (95%CI)	5.1 (4.7-6.2)	5.4 (4.8-6.2)
HR (95%CI)	0.80 (0.66-0.96)	

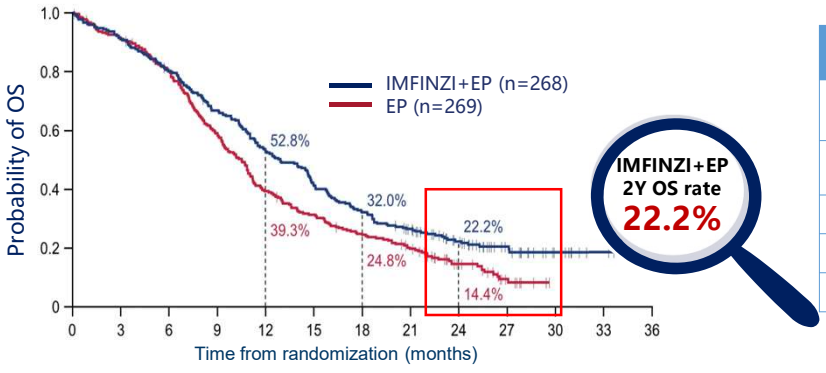
*PFS was not formally tested for statistical significance
*56.8% of patients in the control arm received 6 cycles of EP

Landmark PFS, %	IMFINZI+EP	EP	
6 months	45.4	45.8	
12 months	17.9	5.3	×3
18 months	13.9	3.4	×4
24 months	11.0	2.9	×4

1.Paz-Ares L, et al. 2020 ASCO. Abstract 9002.
2. Jonathan W Goldman, et al. 2020 ESMO. Abstract LBA86

45

IMFINZI+EP: Sustained overall survival benefit at 2 years



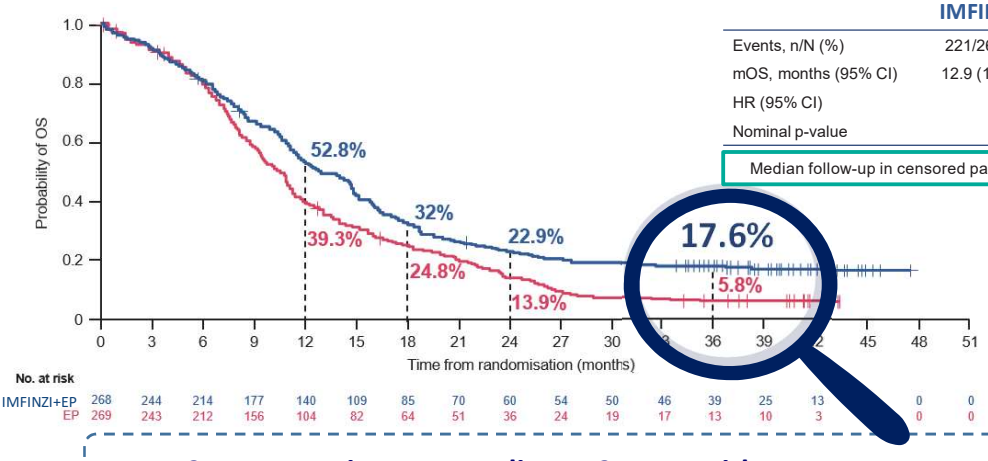
	IMFINZI+EP (n=268)	EP (n=269)
mOS (m) (95%CI)	**12.9** (11.3-14.7)	**10.5** (9.3-11.2)
HR(95%CI) P value	**0.75** (0.62-0.91) 0.0032	
12m OS rate	52.8%	39.3%
18m OS rate	32%	24.8%
24m OS rate	**22.2%**	14.4%

Nearly a quarter of patients were still alive at 24 months with IMFINZI+EP[2]

1. Paz-Ares L, et al. 2020 ASCO. Abstract 9002.
2. Goldman JW, Dvorkin M, Chen Y, et al. Durvalumab, with or without tremelimumab, plus platinum-etoposide in first-line treatment of extensivestage small-cell lung cancer (CASPIAN): updated results from a randomised, controlled, open-label, phase 3 trial. Lancet Oncol. 2020;to be published.

46

IMFINZI + EP: The only IO combination to demonstrate 3-year overall survival in ES-SCLC



	IMFINZI+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)

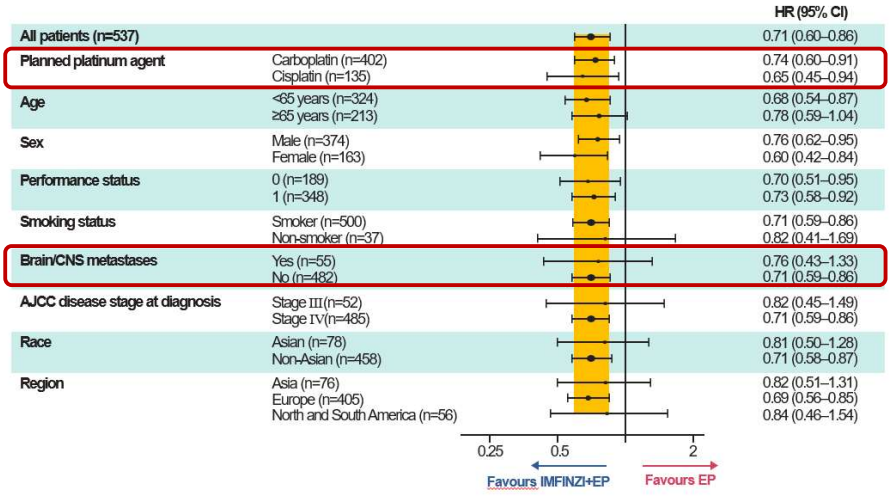
3× more patients were alive at 3 years with IMFINZI + EP vs EP alone

Data cutoff. 22 March 2021

47 Ref:PazAres1 L, Chen Y, Reinmuth N, et al.Durvalumab ± tremelimumab + platinumetoposide in firstline extensive-stage SCLC (ES-SCLC): 3-year overall survival update from the phase III CASPIAN study. 2021 ESMO. LBA61.

47

OS benefit with IMFINZI + EP remained consistent across all subgroups with over 3 years of follow-up[1]



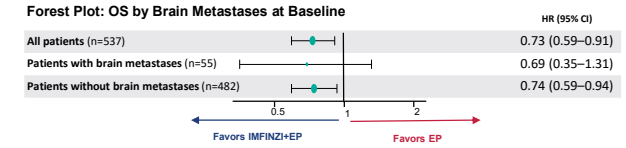
Ref:PazAres1 L, Chen Y, Reinmuth N, et al.Durvalumab ± tremelimumab + platinumetoposide in firstline extensive-stage SCLC (ES-SCLC): 3-year overall survival update from the phase III CASPIAN study. 2021 ESMO. LBA61.

Data cutoff. 22 March 2021; Size of circle is proportional to the number of events across both treatment groups AJCC, American Joint Committee on Cancer, CNS, central nervous system

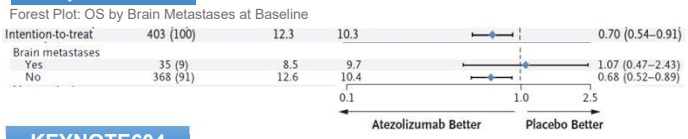
48

CASPIAN/IMPOWER133/KEYNOTE-604 - BM analysis

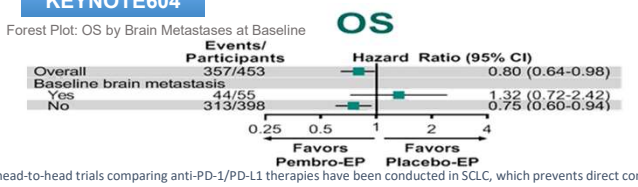
CASPIAN



IMpower133



KEYNOTE604



IMFINZI + EP consistently improved OS versus EP in patients regardless of the presence of baseline brain metastases

[a]No head-to-head trials comparing anti-PD-1/PD-L1 therapies have been conducted in SCLC, which prevents direct comparison of the different anti-PD-1/PD-L1 molecules

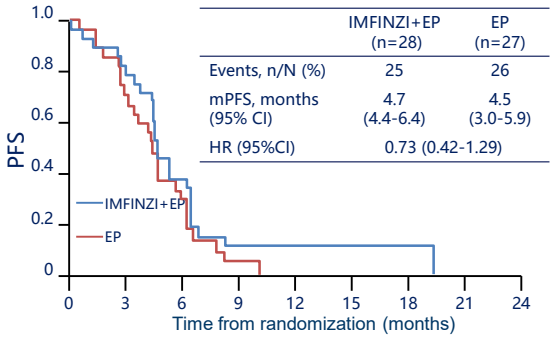
49 1.Chen Y, et al. 2020 ASCO Abstract 9068. 2.Horn L, et al. N Engl J Med 2018;379:2220–2229. 3. Rudin CM, et al. J Clin Oncol 2020;38:abstr 9001

49

CASPIAN: OS & PFS Based on Baseline Brain Metastases

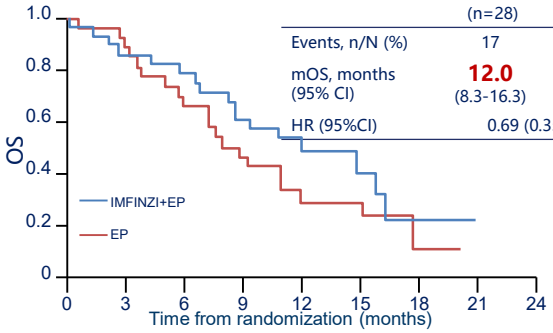
IMFINZI + EP consistently improved OS versus EP in patients regardless of the presence of baseline brain metastases

PFS: With Brain Metastases



	IMFINZI+EP (n=28)	EP (n=27)
Events, n/N (%)	25	26
mPFS, months (95% CI)	4.7 (4.4-6.4)	4.5 (3.0-5.9)
HR (95%CI)	0.73 (0.42-1.29)	

OS: With Brain Metastases



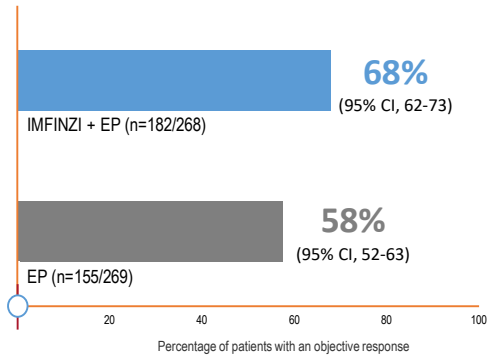
	IMFINZI+EP (n=28)	EP (n=27)
Events, n/N (%)	17	20
mOS, months (95% CI)	**12.0** (8.3-16.3)	8.8 (5.7-11.9)
HR (95%CI)	0.69 (0.35-1.31)	

50 Chen Y et al. Poster presented at: ASCO Virtual Annual Meeting; May 29-31, 2020.

50

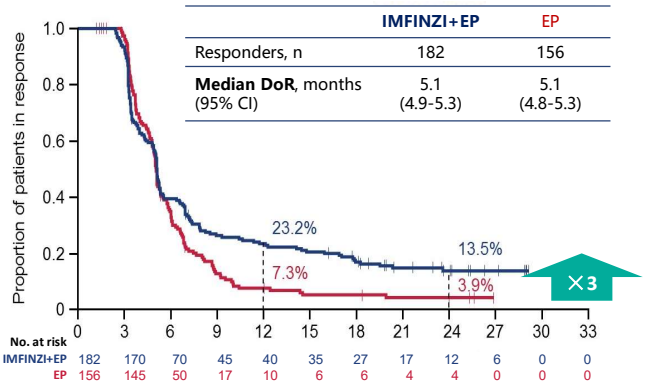
IMFINZI + EP Provided a High Response Rate and Demonstrated Ongoing Responses at 1 Year[1,2,a]

CONFIRMED OBJECTIVE RESPONSE RATE (POST-HOC ANALYSIS)[1,2]



- Complete responses: 2% with IMFINZI + EP and 1% with EP alone[2]
- Partial responses: 66% with IMFINZI + EP and 57% with EP alone[2]

ONGOING RESPONSE RATE AT 12 MONTHS (POST-HOC ANALYSIS)[2,3,4]



	IMFINZI+EP	EP
Responders, n	182	156
Median DoR, months (95% CI)	5.1 (4.9-5.3)	5.1 (4.8-5.3)

- Median DoR: 5.1 months (95% CI, 4.9-5.3) with IMFINZI + EP and 5.1 months (95% CI, 4.8-5.3) for patients treated with EP alone[3]
- At data cutoff, the median duration of follow-up was 14.2 months[2]

[a]Confirmed objective response and duration of confirmed response were analyzed post hoc.[2]

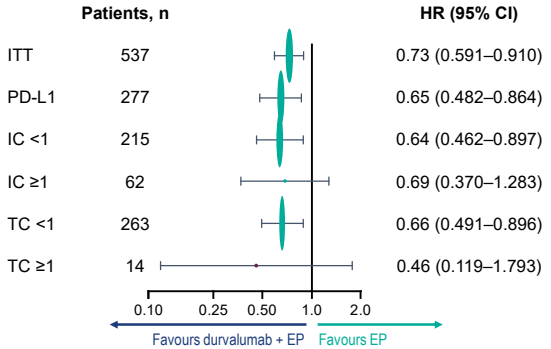
DoR, duration of response; EP, etoposide/platinum-based chemotherapy.

1. IMFINZI® (durvalumab) [Prescribing Information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2020. 2. Paz-Ares L, et al. *Lancet*. 2019;394(10212):1929-1939. 3. Paz-Ares L, et al. Presented at: IASLC 20th WCLC; September 7-10, 2019; Barcelona, Spain. Abstract PL02.11. 4 Paz-Ares L, et al. 2020 ASCO. Abstract 9002.

51

CASPIAN: Interim Analysis (DCO March 11, 2019) – OS Based on PD-L1 Expression[a]

- Durvalumab + EP was associated with improved OS vs EP, irrespective of PD-L1 expression.
- No significant interaction was observed with OS based on PD-L1 expression as a continuous variable (TC; p=0.5354; IC; p=0.2271); similar results were observed with PFS and ORR.



Note: Due to low PD-L1 expression, ≥1% cutoff was used in post-hoc analyses.

[a]Data cutoff: March 11, 2019.

CI = confidence interval; EP = platinum-etoposide; HR = hazard ratio; IC = immune cell; ITT = intent-to-treat; PD-L1 = programmed cell death ligand-1; TC = tumor cell.

Paz-Ares L et al. Presented at: European Society for Medical Oncology (ESMO); September 27-October 1, 2019; Barcelona, Spain.

52

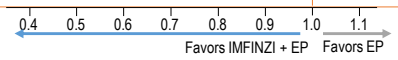
Patient-Reported Outcomes in Prespecified Analyses With IMFINZI + EP: Global Health Status/QoL and Functioning Scales

HRQoL and functioning were assessed using EORTC QLQ-C30[1]

- In the CASPIAN study, global health status/QoL and functioning scores at baseline were comparable between arms[1]
- EORTC QLQ-C30 is an integrated questionnaire for assessing HRQoL of cancer patients participating in clinical trials using a scale of 0 to 100 with high scores representing high or healthy levels of functioning/high QoL[2]
- Clinically meaningful deterioration in HRQoL/functioning was predefined as a decrease from baseline of ≥10 points[1,3,4]
- The QLQ-C30 includes a global health status/QoL scale, 5 functional scales, 3 symptom scales, and 6 single items[2]

TIME TO DETERIORATION IN HRQoL AND FUNCTIONING SCALES[1]

EORTC QLQ-C30	HR (95% CI)
Global health status/QoL (n=470)	0.81 (0.626-1.054)
Cognitive functioning (n=486)	0.61 (0.472-0.776)
Emotional functioning (n=481)	0.61 (0.464-0.800)
Physical functioning (n=483)	0.75 (0.581-0.970)
Role functioning (n=456)	0.71 (0.550-0.904)
Social functioning (n=472)	0.70 (0.549-0.897)



EORTC, European Organization for Research and Treatment of Cancer; EP, etoposide/platinum-based chemotherapy; HR, hazard ratio; HRQoL, health-related quality of life; QoL, quality of life; QLQ-C30, Core Quality of Life Questionnaire 30.

1. Paz-Ares L, et al. Presented at: ESMO Annual Congress; September 27-October 1, 2019; Barcelona, Spain. 2. Fayers PM, et al. The EORTC QLQ-C30 Scoring Manual. 3rd ed. Brussels, Belgium: European Organisation for Research and Treatment of Cancer; 2001. 3. Cocks K, et al. *Eur J Cancer*. 2012;48(11):1713-1721. 4. Osoba D, et al. *J Clin Oncol*. 1998;16(1):139-144.

53

Safety and Tolerability Profile for IMFINZI + EP

ADVERSE REACTIONS REPORTED IN ≥10% OF PATIENTS

	IMFINZI + EP (n=265)		EP (n=266)	
	All grades (%)	Grades 3-4 (%)	All grades (%)	Grades 3-4 (%)
Respiratory, thoracic, and mediastinal disorders				
Cough/productive cough	15	0.8	9	0
Gastrointestinal disorders				
Nausea	34	0.4	34	1.9
Constipation	17	0.8	19	0
Vomiting	15	0	17	1.1
Diarrhea	10	1.1	11	1.1
Endocrine disorders				
Hyperthyroidism[a]	10	0	0.4	0
Skin and subcutaneous tissue disorders				
Alopecia	31	1.1	34	0.8
Rash[b]	11	0	6	0
General disorders and administration site conditions				
Fatigue/asthenia	32	3.4	32	2.3
Metabolism and nutrition disorders				
Decreased appetite	18	0.8	17	0.8

Discontinuation rates[2]: 9% IMFINZI + EP vs 9% WITH EP ALONE

- Incidence of Grade 3 or 4 adverse events was comparable between IMFINZI + EP (62%) and EP alone (62%)[2]
- Serious adverse reactions occurred in 31% of patients receiving IMFINZI + EP. The most frequent serious adverse reactions reported in ≥1% of patients were febrile neutropenia (4.5%), pneumonia (2.3%), anemia (1.9%), pancytopenia (1.5%), pneumonitis (1.1%), and COPD (1.1%)[1]
- Fatal adverse reactions occurred in 4.9% of patients receiving IMFINZI + EP. These include pancytopenia, sepsis, septic shock, pulmonary artery thrombosis, pulmonary embolism, and hepatitis (1 patient each) and sudden death (2 patients)[1]

[a]Includes hyperthyroidism and Basedow's disease. [b]Includes rash erythematous, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, erythema, eczema, rash and dermatitis.
COPD, chronic obstructive pulmonary disease; EP, etoposide/platinum-based chemotherapy.

1. IMFINZI® (durvalumab) [Prescribing Information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2020. 2. Paz-Ares L, et al. *Lancet*. 2019;394(10212):1929-1939.

54

Safety and Tolerability Profile for IMFINZI + EP (cont'd)

LABORATORY ABNORMALITIES WORSENING FROM BASELINE OCCURRING IN ≥20% OF PATIENTS[1,a]		
	IMFINZI + EP	EP
	Grade[b] 3 or 4 (%)[c]	Grade[b] 3 or 4 (%)[c]
Chemistry		
Hyponatremia	11	13
Hypomagnesemia	11	6
Hyperglycemia	5	5
Increased alkaline phosphatase	4.9	3.5
Increased ALT	4.9	2.7
Increased AST	4.6	1.2
Hypocalcemia	3.5	2.4
Blood creatinine increased	3.4	1.1
Hyperkalemia	1.5	3.1
TSH decreased <LLN and ≥LLN at baseline	NA	NA
Hematology		
Neutropenia	41	48
Lymphopenia	14	13
Anemia	13	22
Thrombocytopenia	12	15

- imAEs of any grade were reported in 20% of patients treated with IMFINZI + EP and 3% of patients treated with EP alone[2]
- Early identification and intervention may help manage many imAEs[1,3]

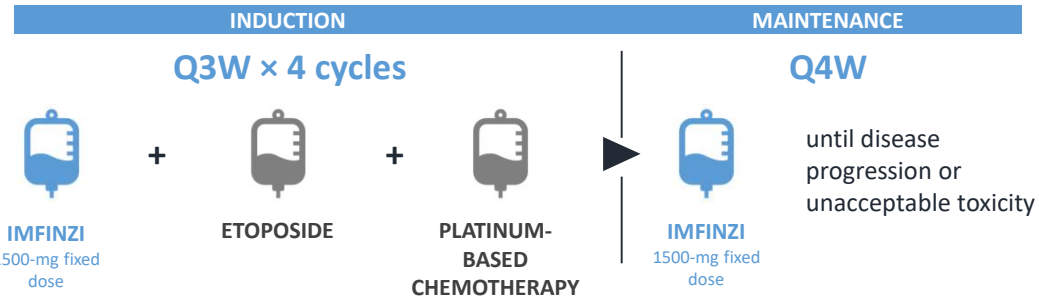
[a]The frequency cut off is based on any grade change from baseline. [b]Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. [c]Each test incidence is based on the number of patients who had both baseline and at least 1 on-study laboratory measurement available: IMFINZI (range: 258 to 263) and chemotherapy (range: 253 to 262) except magnesium: IMFINZI + EP (18) and EP alone (16).

ALT, alanine aminotransferase; AST, aspartate aminotransferase; EP, etoposide/platinum-based chemotherapy; imAE, immune-mediated adverse event; LLN, lower limit of normal; TSH, thyroid-stimulating hormone.

55 1. IMFINZI® (durvalumab) [Prescribing Information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2020. 2. Paz-Ares L, et al. *Lancet*. 2019;394(10212):1929-1939. 3. Daniels GA, et al. *Emerg Med J*. 2019;36(6):369-377.

55

IMFINZI Is Given as a Fixed 1500-mg Dose in the 1L Treatment of ES-SCLC



- Patients with a body weight of ≤30 kg must receive weight-based dosing, equivalent to IMFINZI 20 mg/kg according to the same dosing schedule as above. IMFINZI may be given as 1500-mg fixed dose once body weight increases to >30 kg
- EP consists of etoposide 80 mg/m^2 to 100 mg/m^2 with either carboplatin AUC 5 mg/mL/min or 6 mg/mL/min or cisplatin 75 mg/m^2 to 80 mg/m^2. For more information, please refer to the Prescribing Information for each treatment
  - IMFINZI is administered as a 60-min IV infusion
  - No premedication is required for IMFINZI treatment
  - Administer IMFINZI prior to chemotherapy on the same day

Administer IMFINZI + EP every 3 weeks followed by monthly maintenance with IMFINZI.

56 1L, first line; AUC, area under the curve; EP, etoposide/platinum-based chemotherapy; ES-SCLC, extensive-stage small cell lung cancer; IV, intravenous; Q3W, every 3 weeks; Q4W, every 4 weeks.
IMFINZI® (durvalumab) [Prescribing Information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2020.

56

CASPIAN Study Design Relative to Other 1L ES-SCLC IO Trials

	CASPIAN	IMpower133
Study design	Phase 3, Open-label	Phase 3, placebo-controlled
Maint. schedule	Q4W	Q3W
Chemo cycles	4 cycles for IO arms; up to 6 cycles in control	4 cycles for all arms
Cisplatin option	Cisplatin or Carboplatin	Carboplatin
Asymptomatic untreated brain mets	V	X
PCI in IO arm	X	V
Median Follow-up	39.4 months	22.9 months

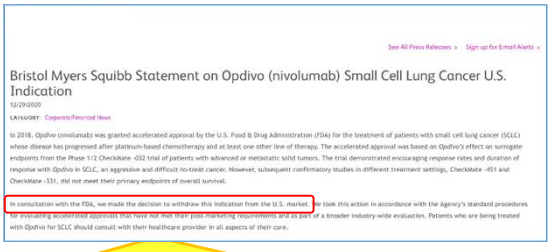
[a]No head-to-head trials comparing anti-PD-1/PD-L1 therapies have been conducted in SCLC, which prevents direct comparison of the different anti-PD-1/PD-L1 molecules

1. AstraZeneca. Data on file; 2. Paz-Ares L, et al. *J Clin Oncol* 2020;38:abstr 9002; 3. Horn L, et al. *N Engl J Med* 2018;379:2220–2229; 4. Reck M, et al. Presented at European Society of Medical Oncology Congress; September 27th – October 1st, 2019; Barcelona, Spain; 5. ClinicalTrials.gov. Available at: www.clinicaltrials.gov/ct2/show/NCT03066778 (Accessed January 2020); 6. Rudin CM, et al. *J Clin Oncol* 2020;38:abstr 9001.

57

Nivolumab & Pembrolizumab has withdrawn ES-SCLC 3L indication

CheckMate-451 & CheckMate-331 didn't meet the primary endpoints.



Bristol Myers Squibb Statement on Opdivo (nivolumab) Small Cell Lung Cancer U.S. Indication

12/29/2020

CATEGORY: Corporate/Financial News

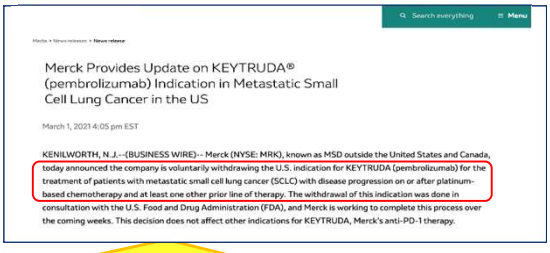
In 2018, Opdivo (nivolumab) was granted accelerated approval by the U.S. Food & Drug Administration (FDA) for the treatment of patients with small cell lung cancer (SCLC) whose disease has progressed after platinum-based chemotherapy and at least one other line of therapy. The accelerated approval was based on Opdivo's effect on surrogate endpoints from the Phase 1/2 CheckMate -032 trial of patients with advanced or metastatic solid tumors. The trial demonstrated encouraging response rates and duration of response with Opdivo in SCLC, an aggressive and difficult-to-treat cancer. However, subsequent confirmatory studies in different treatment settings, CheckMate -451 and CheckMate -331, did not meet their primary endpoints of overall survival.

In consultation with the FDA, we made the decision to withdraw this indication from the U.S. market. We took this action in accordance with the Agency's standard procedures for evaluating accelerated approvals that have not met their post-marketing requirements and as part of a broader industry-wide evaluation. Patients who are being treated with Opdivo for SCLC should consult with their healthcare provider in all aspects of their care.

In consultation with the FDA, we made the decision to withdraw this indication from the US's market.

Nivolumab received accelerated approval from the FDA in 2018 based on data from surrogate end points of the phase 1/2 CheckMate-032 clinical trial in patients with advanced or metastatic solid tumors.

KEYNOTE-604 didn't meet the primary endpoints.



Search everything Menu

Merck Provides Update on KEYTRUDA® (pembrolizumab) Indication in Metastatic Small Cell Lung Cancer in the US

March 1, 2021 4:05 pm EST

KENILWORTH, N.J.--(BUSINESS WIRE)-- Merck (NYSE: MRK), known as MSD outside the United States and Canada, today announced the company is voluntarily withdrawing the U.S. indication for KEYTRUDA (pembrolizumab) for the treatment of patients with metastatic small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy. The withdrawal of this indication was done in consultation with the U.S. Food and Drug Administration (FDA), and Merck is working to complete this process over the coming weeks. This decision does not affect other indications for KEYTRUDA, Merck's anti-PD-1 therapy.

The company is voluntarily withdrawing the U.S. indication for KEYTRUDA(pembrolizumab) for the treatment of patients with metastatic small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.

Pembrolizumab was initially granted accelerated approval in 2019 for patients with SCLC following disease progression on or after frontline platinum-based chemotherapy and at least 1 other therapy.[2] Efficacy was based on results from the phase 1 KEYNOTE-28 (NCT02054806) and the phase 2 KEYNOTE-158 (NCT02628067) trials.

https://news.bms.com/news/corporate-financial/2020/Bristol-Myers-Squibb-Statement-on-Opdivo-nivolumab-Small-Cell-Lung-Cancer-US-Indication/default.aspx
https://www.merck.com/news/merck-provides-update-on-keytruda-pembrolizumab-indication-in-metastatic-small-cell-lung-cancer-in-the-us/

58

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2022
Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY

SCLC SUBSEQUENT SYSTEMIC THERAPY (PS 0–2)[c] Consider dose reduction or growth factor support for patients with PS 2.	
Relapse ≤6 months	**Relapse >6 months**
Preferred Regimens • Topotecan PO or IV[14-16] • Lurbinectedin[17] • Clinical trial **Other Recommended Regimens** • Paclitaxel[18,19] • Docetaxel[20] • Irinotecan[21] • Temozolomide[22,23] • Cyclophosphamide/doxorubicin/vincristine (CAV)[14] • Oral etoposide[24,25] • Vinorelbine[26,27] • Gemcitabine[28,29] • Nivolumab[b,d,30,31] • Pembrolizumab[b,d,32-34] • Bendamustine (category 2B)[35]	**Preferred Regimens** • Original regimen[d,36,37] **Other Recommended Regimens** • Topotecan PO or IV[14-16] • Paclitaxel[18,19] • Docetaxel[20] • Irinotecan[21] • Temozolomide[22,23] • CAV[14] • Oral etoposide[24,25] • Vinorelbine[26,27] • Gemcitabine[28,29] • Nivolumab[b,d,30,31] • Pembrolizumab[b,d,32-34] • Lurbinectedin[38] • Bendamustine (category 2B)[35]

NCCN guideline 2022.V2

59

Summary

- IMFINZI + EP: The only IO combination to demonstrate unprecedented 3-year overall survival in ES-SCLC
- 3× more patients were alive at 3 years with IMFINZI + EP vs EP alone (17.6% vs 5.8%)
- The CASPIAN trial was designed to reflect real-world clinical practice
- OS benefit with IMFINZI + EP remained consistent across all subgroups with over 3 years of follow-up (Cis/Carbo)
- IMFINZI + EP consistently improved OS versus EP in patients regardless of the presence of baseline brain metastases

60

61