SCLC From Benchside to Bedside

ΕΛΕΥΘΕΡΙΑΔΟΥ ΕΛΛΑΔΑ

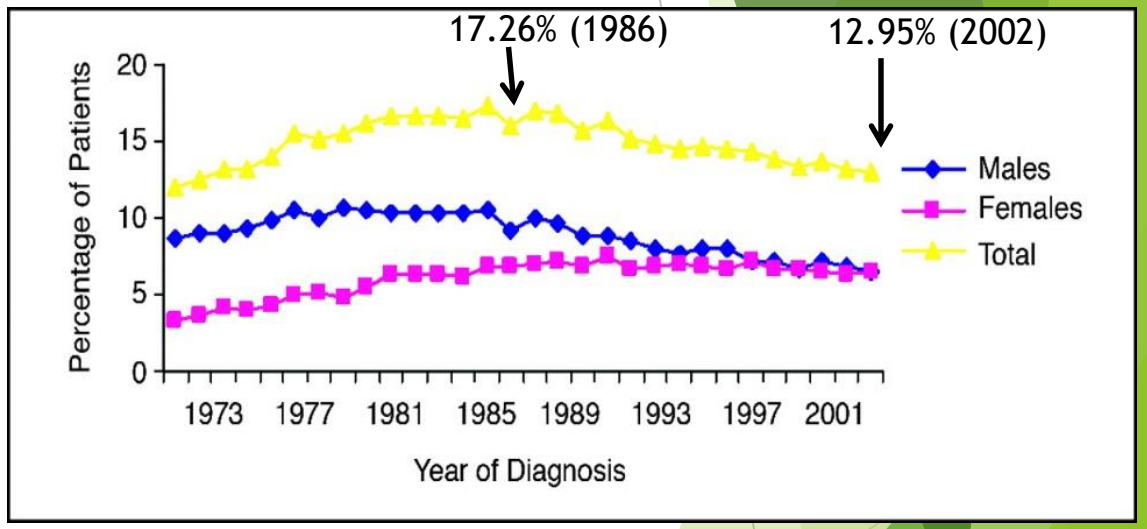
ΠΝΕΥΜΟΝΟΛΟΓΟΣ, MD, Phd

ΥΠΟΤΡΟΦΟΣ ΑΠΘ,ΠΑΝΕΠΙΣΤΙΜΙΑΚΗ ΠΝΕΥΜΟΝΟΛΟΓΙΚΗ ΚΛΙΝΙΚΗ ,Γ.Ν.ΠΑΠΑΝΙΚΟΛΑΟΥ.

«**Best of 19th IASLC World Conference on Lung Cancer, WCLC 2018**».17 -18 Μαΐου 2019

SCLC: A Recalcitrant Cancer

- >200,000 cases/year globally
- ~98% tobacco-related
- Two-thirds present with Stage IV SCLC
- First-line chemotherapy:
  - RR 60-80%
  - Median OS 7-10 months
  - 1-year OS 35-40%
  - 2-year OS ~5%



- Incidence dropping in high income countries related to changes in tobacco exposure, likely rising in LMIC

OS: overall survival; LMIC: low and middle income countries

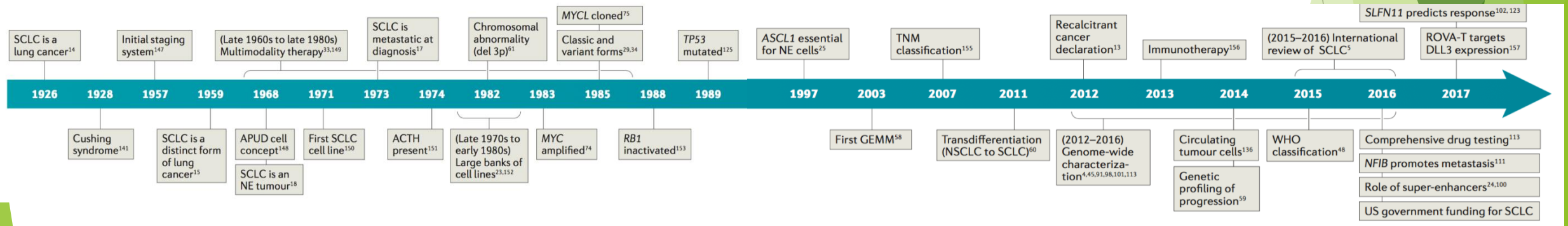
Chute et al J Clin Oncol 1999; Govindan et al J Clin Oncol 2006; Subramanian & Govindan, Nat Rev Clin Oncol 2010

Improving Survival in Stage IV SCLC: A Long Journey

Third line — Nivolumab*

Second line — Topotecan* or CAV; Amrubicin

First line — Single agent chemotherapy; Combination chemotherapy; **Etoposide/platinum**; CAV/CEV; PCI; **Irinotecan /platinum**; TRT



CAV/CEV: cyclophosphamide, doxorubicin/epirubicin, vincristine; PCI: prophylactic cranial irradiation; RTR: thoracic radiotherapy; *US Food and Drug Administration approved

Gazdar et al Nat Rev Cancer 2017; Haddadin & Perry Clin Lung Cancer 2011; Leighl J Clin Oncol 2015; Roth et al J Clin Oncol 1992; Arriagada et al. J Natl Cancer Inst 1995;Slotman et al NEJM 2007; Seto et al J Clin Oncol; Noda et al NEJM 2002; Hanna et al J Clin Oncol 2006; Lara et al. J Clin Oncol 2009; Slotman et al. Lancet 2015; Von Pawel et al, J Clin Oncol 1999; O'Brien et al. J Clin Oncol 2006; Von Pawel J Clin Oncol 2014; Antonia et al. Lancet Oncol 2016

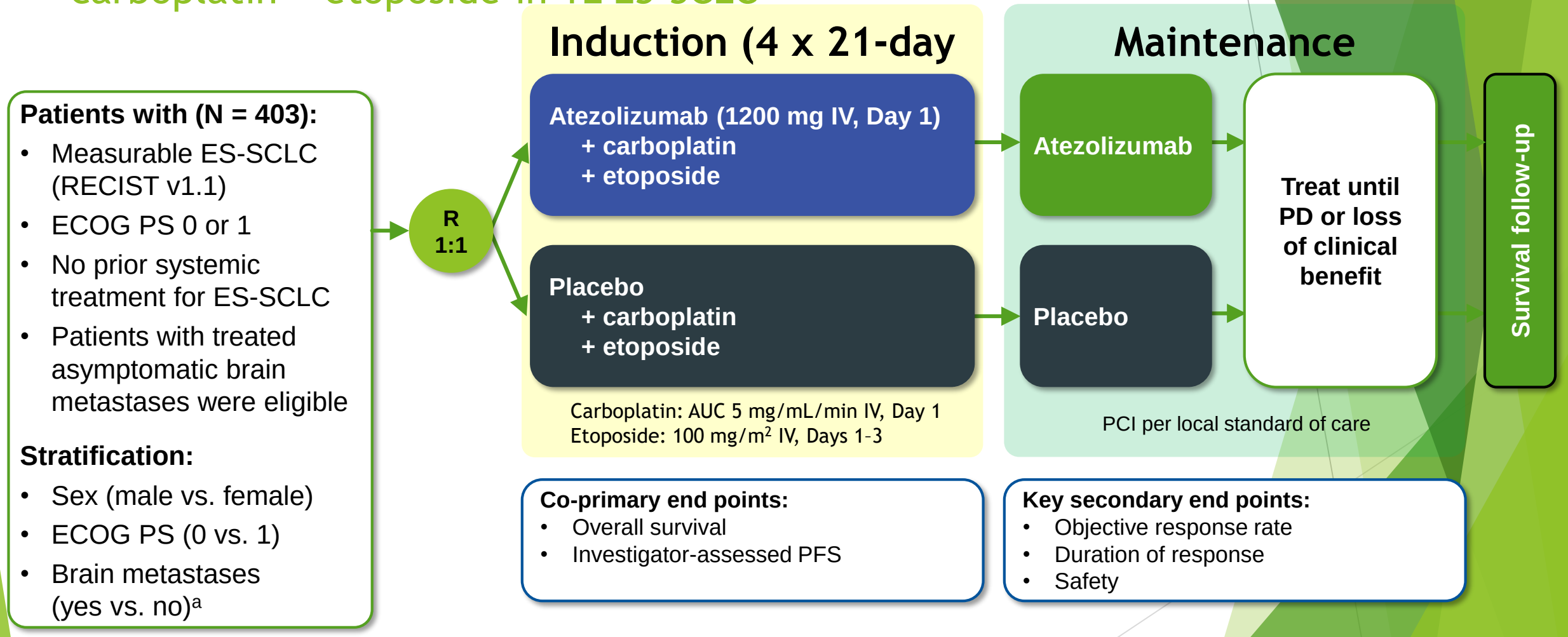
Background

- There has been little progress in the 1L treatment of ES-SCLC in over 20 years
  - The majority of patients present with ES-SCLC; 1L standard of care remains platinum (carboplatin or cisplatin) plus etoposide[1–4]
  - Outcomes remain poor, with a median OS of ~10 months[4,5]
- Immunotherapy has shown clinical activity in refractory or metastatic SCLC[6–8]
  - Nivolumab has been approved in the 3L treatment of metastatic SCLC as a single agent[9]
  - Preclinical data suggest possible synergy between anti–PD-L1 treatment and chemotherapy[10]
- IMpower133 (NCT02763579) evaluated the efficacy and safety of 1L atezolizumab, a humanized monoclonal anti–PD-L1 antibody, or placebo, plus carboplatin and etoposide in ES-SCLC

1L, first-line; 3L, third-line; ES-SCLC, extensive-stage small cell lung cancer; OS, overall survival; PD-L1, programmed death-ligand 1.

1. Evans WK, et al. *J Clin Oncol,* 1985. 2. NCCN clinical practice guidelines in oncology. Small cell lung cancer. V2.2018. https://www.nccn.org/professionals/physician_gls/pdf/sclc.pdf. Updated 2018. Accessed May 23, 2018. 3. Stahel R, et al. *Ann Oncol,* 2011. 4. Farago AF, Keane FK. *Transl Lung Cancer Res*, 2018. 5. Socinski MA, et al. *J Clin Oncol*, 2009. 6. Antonia SJ, et al. *Lancet Oncol*, 2016. 7. Sequist LV, et al. *Ann Oncol*, 2016 (Suppl 6). 8. Gadgeel SM, et al. *J Thoracic Oncol*, 2018. 9. OPDIVO® (nivolumab) [prescribing information]. Bristol-Myers Squibb, 2018. 10. Camidge R, et al. *J Thoracic Oncol*, 2015.

IMpower133: Global Phase 1/3, double-blind, randomized, placebo-controlled trial evaluated atezolizumab + carboplatin + etoposide in 1L ES-SCLC



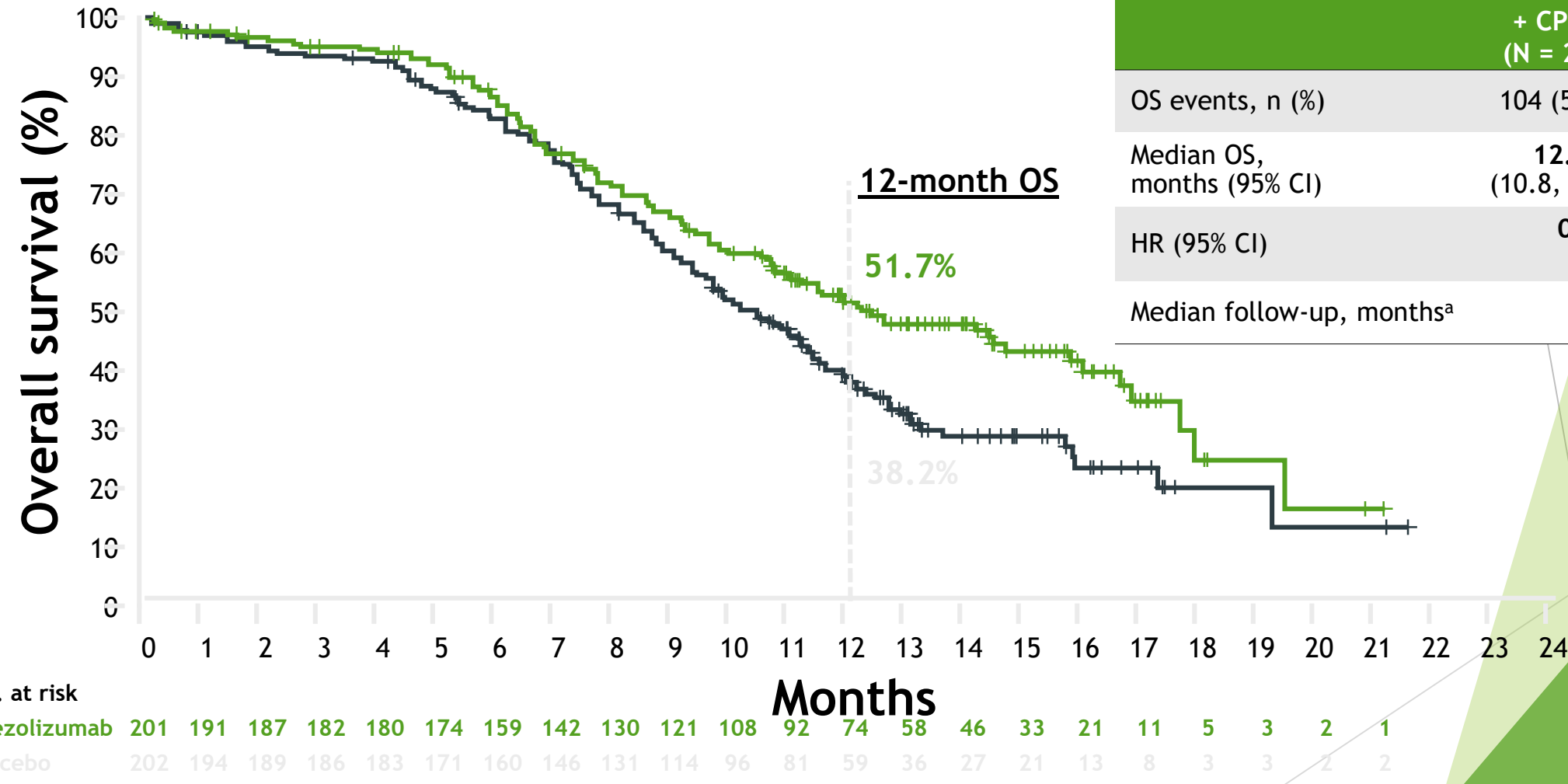
[a] Only patients with treated brain metastases were eligible. ECOG PS, Eastern Cooperative Oncology Group Performance Status; IV, intravenous; PCI, prophylactic cranial irradiation; PD, progressive disease; PFS, progression-free survival; R, randomized; RECIST, Response Evaluation Criteria In Solid Tumors.

Baseline characteristics

Characteristic	Atezolizumab + CP/ET (N = 201)	Placebo + CP/ET (N = 202)
Median age (range) — years	64 (28–90)	64 (26–87)
Age group — no. (%)		
< 65 years	111 (55)	106 (52)
≥ 65 years	90 (45)	96 (48)
Male sex — no. (%)[a]	129 (64)	132 (65)
Smoking status[b]		
Current smoker	74 (36.8)	75 (37.1)
Former smoker	118 (58.7)	124 (61.4)
Race — no. (%)		
White	163 (81)	159 (79)
Asian	33 (16)	36 (18)
Other	5 (2)	7 (3)
ECOG PS — no. (%)[a]		
0	73 (36)	67 (33)
1	128 (64)	135 (67)
Brain metastases — no. (%)[a]		
Yes	17 (8)	18 (9)
Liver metastases — no. (%)		
Yes	77 (38)	72 (36)

Clinical data cutoff date: April 24, 2018. [a] Data reported per electronic case report form. [b] Nine patients in the atezolizumab group and three patients in the placebo group have never smoked.
CP/ET, carboplatin + etoposide.

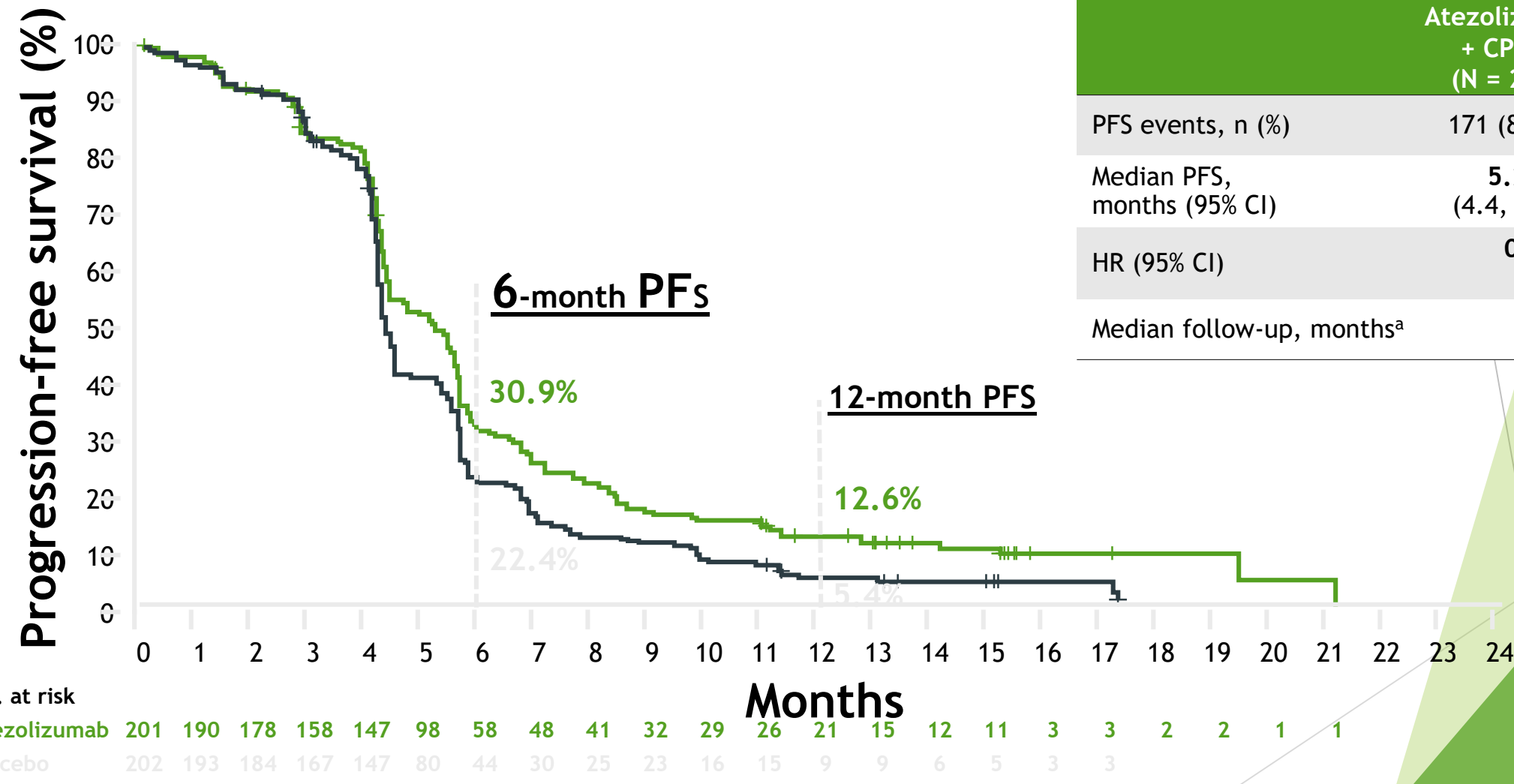
Overall survival



	Atezolizumab + CP/ET (N = 201)	Placebo + CP/ET (N = 202)
OS events, n (%)	104 (51.7)	134 (66.3)
Median OS, months (95% CI)	**12.3** (10.8, 15.9)	**10.3** (9.3, 11.3)
HR (95% CI)	**0.70** (0.54, 0.91) p = 0.0069	
Median follow-up, months[a]	13.9	

[a] Clinical data cutoff date: April 24, 2018, 11 months after the last patient was enrolled. CI, confidence interval; HR, hazard ratio; CP/ET, carboplatin + etoposide.

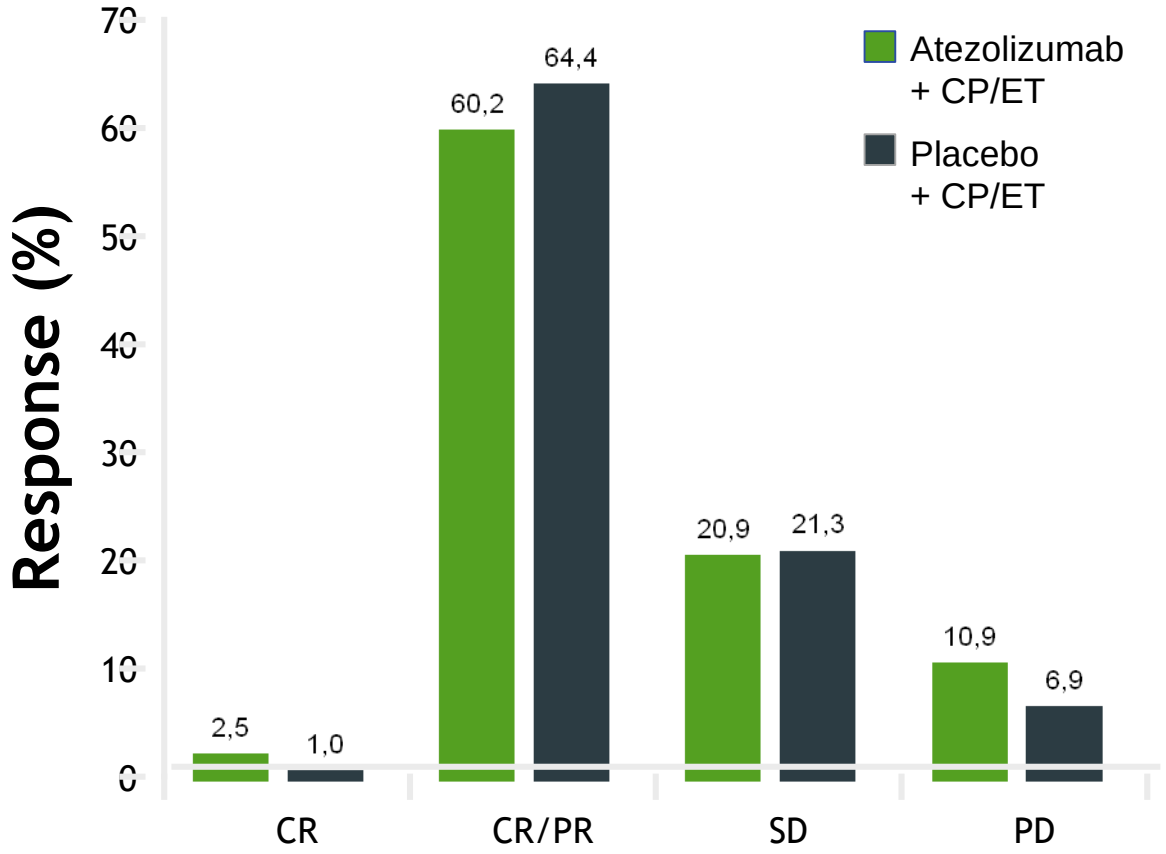
Investigator-assessed progression-free survival



	Atezolizumab + CP/ET (N = 201)	Placebo + CP/ET (N = 202)
PFS events, n (%)	171 (85.1)	189 (93.6)
Median PFS, months (95% CI)	**5.2** (4.4, 5.6)	**4.3** (4.2, 4.5)
HR (95% CI)	**0.77** (0.62, 0.96) p = 0.017	
Median follow-up, months[a]	13.9	

[a] Clinical data cutoff date: April 24, 2018, 11 months after the last patient was enrolled. CI, confidence interval; HR, hazard ratio; CP/ET, carboplatin + etoposide.

Confirmed objective response and duration of response

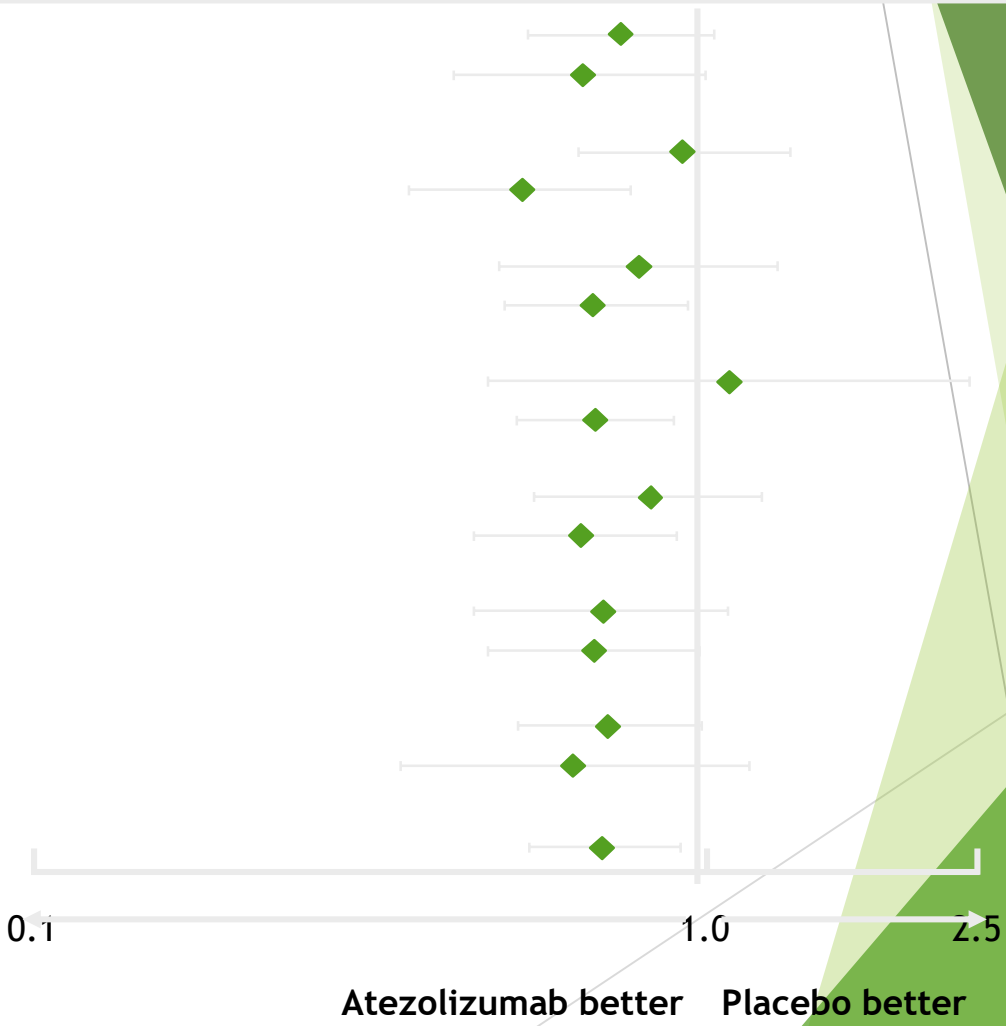


Duration of response	Atezolizumab + CP/ET (N = 121)	Placebo + CP/ET (N = 130)
Median duration, months (range)	4.2 (1.4[a] to 19.5)	3.9 (2.0 to 16.1[a])
HR (95% CI)	0.70 (0.53, 0.92)	
6-month event-free rate — %	32.2	17.1
12-month event-free rate — %	14.9	6.2
Patients with ongoing response — no. (%)[b]	18 (14.9)	7 (5.4)

[a] Censored. [b] At clinical cutoff date: April 24, 2018. CR, complete response; EFS, event-free survival; PD, progressive disease; PR, partial response; SD, stable disease.

Overall survival in key subgroups

Population	Median overall survival (months) Atezolizumab + CP/ET	Placebo + CP/ET	OS hazard ratio[a] (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 years (n = 217)	12.1	11.5	0.92 (0.64, 1.32)
≥ 65 years (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)



Clinical data cutoff date: April 24, 2018. bTMB (blood tumor mutational burden) assessed as reported in Gandara DR, et al. *Nat Med,* 2018.

[a] Hazard ratios are unstratified for patient subgroups and stratified for the ITT.

Safety summary

Patients — no. (%)	Atezolizumab + CP/ET (N = 198)	Placebo + CP/ET (N = 196)
Patients with ≥ 1 AE	198 (100)	189 (96.4)
Grade 3–4 AEs	133 (67.2)	125 (63.8)
Treatment-related AEs[a]	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 treatment[a]	22 (11.1)	6 (3.1)
AEs leading to withdrawal from atezolizumab/placebo	21 (10.6)	5 (2.6)
AEs leading to withdrawal from carboplatin	5 (2.5)	1 (0.5)
AEs leading to withdrawal from etoposide	8 (4.0)	2 (1.0)
Treatment-related deaths	3 (1.5)	3 (1.5)

- Median duration of treatment with atezolizumab was 4.7 months (range: 0 to 21)
- Median number of doses received:
  - Atezolizumab: 7 (range: 1 to 30)
  - Chemotherapy: 4 doses for carboplatin; 12 doses for etoposide (same for both treatment groups)

Clinical data cutoff date: April 24, 2018. Multiple occurrences of the same AE in one patient were counted once at the highest grade for the preferred term.
[a] Incidence of treatment-related AEs and AEs leading to withdrawal from any treatment are for any treatment component. AE, adverse event.

Most frequently observed AEs

Treatment-related AEs — no. (%) > 5% Grade 3-4 AEs in either treatment group	Atezolizumab + CP/ET (N = 198)			Placebo + CP/ET (N = 196)		
	Grade 1-2	Grade 3-4	Grade 5	Grade 1-2	Grade 3-4	Grade 5
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
Neutrophil count decreased	7 (3.5)	28 (14.1)	0	12 (6.1)	33 (16.8)	0
Thrombocytopenia	12 (6.1)	20 (10.1)	0	14 (7.1)	15 (7.7)	0
Leukopenia	15 (7.6)	10 (5.1)	0	10 (5.1)	8 (4.1)	0
Febrile neutropenia	0	6 (3.0)	0	0	12 (6.1)	0

Immune-related AEs — no. (%) > 1% Grade 3-4 AEs in either treatment group	Atezolizumab + CP/ET (N = 198)			Placebo + CP/ET (N = 196)		
	Grade 1-2	Grade 3-4	Grade 5	Grade 1-2	Grade 3-4	Grade 5
Rash	33 (16.7)	4 (2.0)	0	20 (10.2)	0	0
Hepatitis	11 (5.6)	3 (1.5)	0	9 (4.6)	0	0
Infusion-related reaction	7 (3.5)	4 (2.0)	0	9 (4.6)	1 (0.5)	0
Pneumonitis	3 (1.5)	1 (0.5)	0	3 (1.5)	2 (1.0)	0
Colitis	1 (0.5)	2 (1.0)	0	0	0	0
Pancreatitis	0	1 (0.5)	0	0	2 (1.0)	0

Clinical data cutoff date: April 24, 2018.

Summary

- IMpower133 is the first study in over 30 years to show a clinically meaningful improvement in OS over the current standard-of-care in 1L ES-SCLC
- The addition of atezolizumab to carboplatin and etoposide provided a significant improvement in OS and PFS, compared with carboplatin and etoposide alone in 1L ES-SCLC
  - mOS: 12.3 vs. 10.3 months; HR: 0.70 (*P* = 0.0069)
  - mPFS: 5.2 vs. 4.3 months; HR: 0.77 (*P* = 0.017)
- The safety profile of atezolizumab plus carboplatin and etoposide was as expected with no new findings
  - Rates of hematologic side effects were similar between treatment groups, and the incidence and types of immune-related AEs were similar to those seen with atezolizumab monotherapy[1–3]
- These data suggest that atezolizumab plus carboplatin and etoposide is a new standard of care for 1L ES-SCLC

m, median.

1. Rittmeyer A, et al. *Lancet*, 2017.
2. Cortinovis D, et al. *Ann Oncol*, 2017 (Suppl. 5).
3. Fehrenbacher L, et al. *Lancet*, 2016.

PCI in SCLC

- High propensity brain metastasis (BM)
  - 65% BM in autopsy studies, 80% in ≥ 2 years survivors

(Nugent, Cancer 1979)

- Limited stage (LS) SCLC with response to treatment
  - ↓ BM (3-year: 59% vs. 33%)
  - ↑ OS (3-year: 15% vs. 21%) *(Aupérin; Meta-analysis NEJM 1999)*

- Extensive-stage (ES) SCLC with response to treatment
  - ↓ BM (1-year: 40% vs. 15%)
  - ↑ OS (1-year: 27% vs. 13%) *(Slotman; NEJM 2007)*

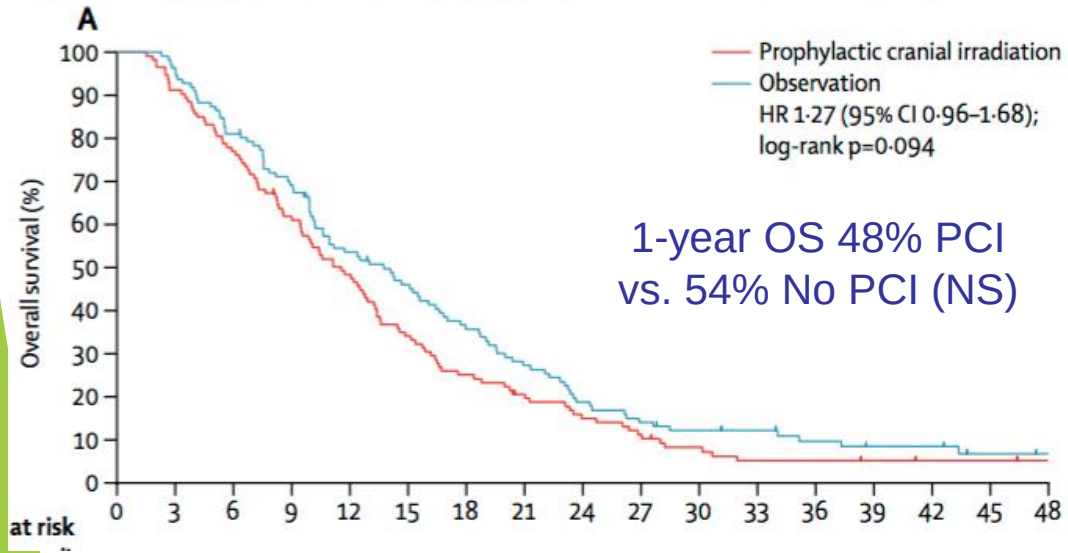
Still a Benefit in Era of Brain MRI?

Prophylactic cranial irradiation versus observation in patients with extensive-disease small-cell lung cancer: a multicentre, randomised, open-label, phase 3 trial

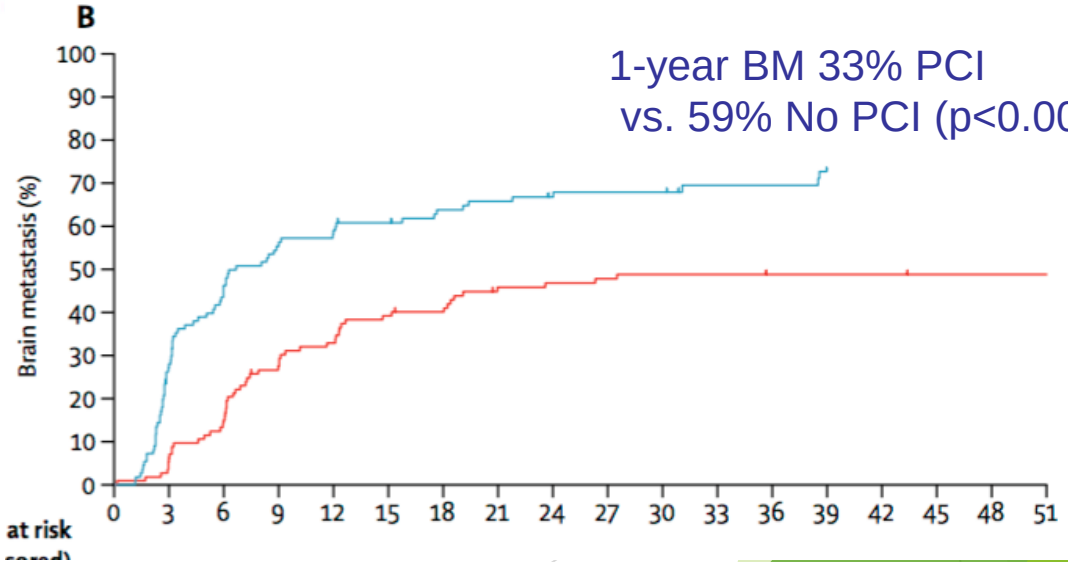
Lancet Oncol, 2017

Toshiaki Takahashi, Takeharu Yamanaka, Takashi Seto, Hideyuki Harada, Hiroshi Nokihara, Hideo Saka, Makoto Nishio, Hiroyasu Kaneda, Koichi Takayama, Osamu Ishimoto, Koji Takeda, Hiroshige Yoshioka, Motoko Tachihara, Hiroshi Sakai, Koichi Goto, Nobuyuki Yamamoto

- Initial/follow-up MRI
- 25 Gy/10 fractions



1-year OS 48% PCI
vs. 54% No PCI (NS)



1-year BM 33% PCI
vs. 59% No PCI (p<0.0001)

NCCN guidelines recommend MRI surveillance when PCI is omitted

Prevalence, Distribution and Risk Factors of Brain Metastases in Limited Stage SCLC Immediately before Prophylactic Cranial Irradiation

Xiao Chu[1, 2] Xi Yang[1, 2] Zhengfei Zhu[1, 2]
[1]Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai, China.

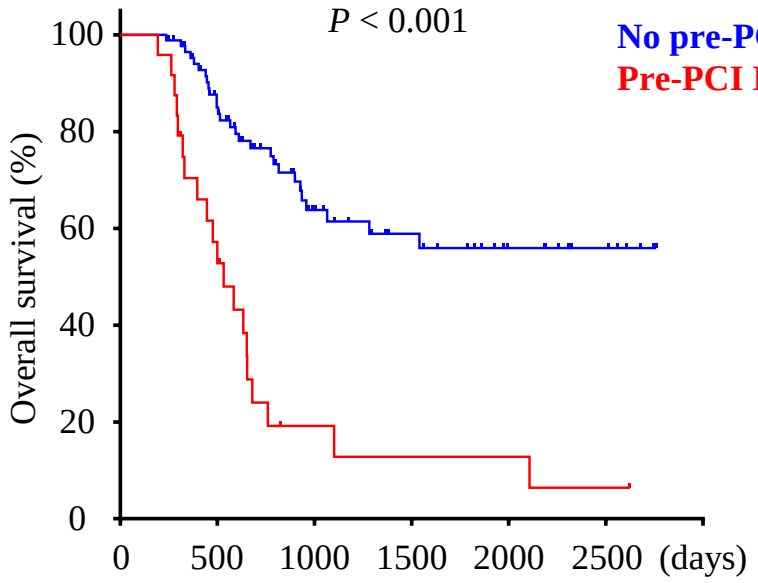
Results: pre-PCI BM prevalence and risk factors

- 110 consecutive LS-SCLC patients receiving PCI after definitive chemoradiotherapy (CRT)
- All with baseline and pre-PCI contrast-enhanced cranial MRI
- **24 (21.8%) harbored pre-PCI BM**
- 23 were asymptomatic
- Median follow-up 2.6 years

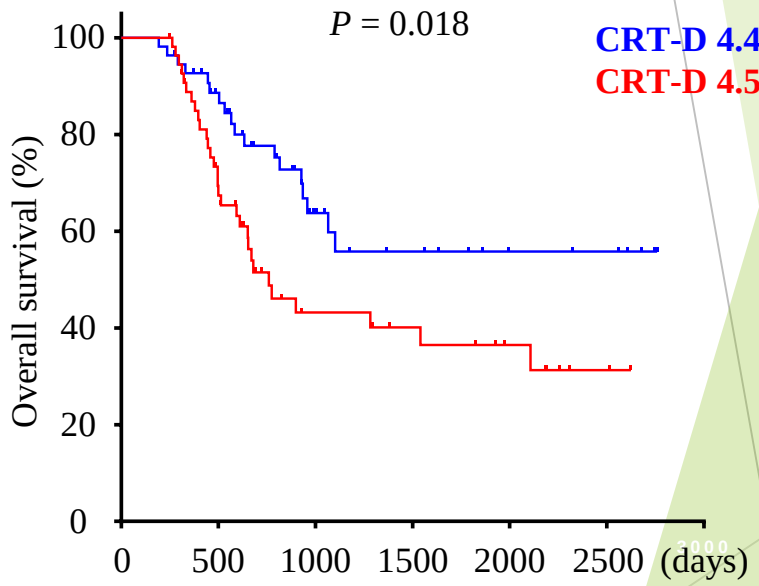
Covariates	RR (95% CI)	*P*
Age at diagnosis	0.966 (0.911 - 1.025)	0.256
Gender	0.358 (0.019 - 6.778)	0.493
Smoking	10.244 (0.567 - 185.146)	0.115
Tumor stage (1-2 vs 3-4)	1.145 (0.424 - 3.093)	0.789
supraclavicular nodes (neg vs pos)	1.354 (0.445 - 4.122)	0.594
CRT-D (months)	1.422 (1.017 - 1.990)	0.040*

CRT-D: chemoradiotherapy duration. Binary logistic regression was employed for analysis.

Results: Impact of pre-PCI BM and CRT duration on LS-SCLC survival



No. at risk						
No pre-PCI BM	86	64	29	20	11	6
Pre-PCI BM	24	13	3	2	2	1



No. at risk						
CRT-D 4.4 months or shorter	55	42	18	11	6	5
CRT-D 4.5 months or longer	55	35	14	11	7	2

Both confirmed by multivariate cox regression

Conclusions

- A substantial proportion of LS-SCLC patients harbor occult brain lesions before scheduled PCI.
- CRT duration is an independent risk factor for pre-PCI BM and OS.
- Early PCI should be considered in LS-SCLC (eradicates micro-lesions before they become overt).

Should stereotactic radiosurgery be considered for salvage of intracranial recurrence in small cell lung cancer?

B Mazure, N Guest, A Letcher, S Ghosh, Z Gabos, KP Chu, B Debenham, T Nijjar, D Severin, R Scrimger, W Roa, D Yee, A Fairchild.

Cross Cancer Institute, Edmonton, AB, Canada

Methods

- Retrospective population-based review
- Pathologically or cytologically confirmed SCLC
- Experienced ICR after PCI between 01/2013-12/2015
- Eligibility for salvage SRS retrospectively evaluated

Results: LS-SCLC Retrospective SRS Eligibility

- 18.1% (13/72) LS recurred post-PCI
- Median of 11.5 mos (range 6.9-60.9 mos).

	Parameter	N
ECOG **Estimated**	0-2	10
Number of BM	≤ **10**	8
Size of largest BM	≤ **5**cm	6
Systemic disease	Controlled, **controllable** or absent	11
	Met all Criteria	**5**

Results: ES-SCLC Retrospective SRS Eligibility

- 19.4% (19/98) ES recurred post-PCI
- Median of 8.5 mos (range 2.7-26.4 mos).

	Parameter	N
ECOG **Estimated**	0-2	16
Number of BM	≤ **10**	13
Size of largest BM	≤ **5**cm	12
Systemic disease	Controlled, **controllable** or absent	16
	Met all Criteria	**8**

Take Home Messages

- This population-based cohort seems to challenge the nihilistic view of characteristics of intracranial recurrence after PCI.
- With potential for survival exceeding 6 months, repeat irradiation encompassing the whole brain risks meaningful neurocognitive toxicity.
- Approximately 40% of SCLC patients who experience ICR post-PCI may be candidates for salvage SRS

Conclusions

- Atezolizumab +C/E represents a new standard of care for ES-SCLC
- If brain mets develop “early,” prognosis for the patient is poor
- Post-PCI, SRS may be palliative option for SCLC pts

Retreatment with Platinum-Etoposide and Treatment Beyond Second Line

Retreatment with Platinum and Etoposide

- Evolved as “empirical” practice based on concept of Platinum sensitivity/resistant
  - Evidence based on small trials, patients not initially treated with platinum etoposide
  - Randomized phase III trials with re-challenge with Platinum-Etoposide as standard arm not available.
  - Definition or cut-off to define platinum sensitive SCLC varies
    - 60 days, 90 days/ 3months, or 6 months

patients; therefore, they must be watched carefully during treatment to avoid excessive risk.

Greater attention to the needs and support systems of elderly patients is recommended to provide optimal care. Overall, elderly patients have a similar prognosis as stage-matched younger patients. Randomized trials have indicated that less-intensive treatment (eg, single-agent etoposide) is inferior to combination chemotherapy (eg, platinum plus etoposide) in elderly patients with good PS (0–2).[120,121] Several other strategies have been evaluated in elderly patients with SCLC.[79,122-124] The use of 4 cycles of carboplatin plus etoposide seems to yield favorable results, because the area-under-the-curve (AUC) dosing of carboplatin takes into account the declining renal function of the aging patient.[124] However, targeting carboplatin to an AUC of 5, rather than 6, may be more reasonable in this population.[125] The usefulness of short-course, full-intensity chemotherapy has also been explored in elderly or infirm patients, and the results with only 2 cycles of chemotherapy seem to be acceptable, although this approach has not been directly compared with standard therapy.[126]

Second-Line and Third-Line (Subsequent) Therapy

Although SCLC is very responsive to initial treatment, most patients relapse with relatively resistant disease.[127,128] These patients have a median survival of only 4 to 5 months when treated with further chemotherapy. Second-line and third-line (ie, subsequent) chemotherapy provides significant palliation in many patients, although the likelihood of response is highly dependent on the time from initial therapy to relapse. If this interval is less than 3 months (refractory or resistant disease), response to most agents or regimens is poor (≤10%). If more than 3 months have elapsed (sensitive disease), expected response rates are approximately 25%. If patients relapse more than 6 months after first-line treatment, then treatment with their original regimen is recommended.[7,129]

Subsequent chemotherapy generally involves single-agent therapy. Based on phase II trials, active subsequent agents include paclitaxel, docetaxel, topotecan, irinotecan, vinorelbine, gemcitabine, ifosfamide, temozolomide, and oral etoposide.[71,130-134] Preliminary data suggest that temozolomide may be useful for patients with SCLC, especially those with brain metastases and methylated O6-methylguanine-DNA methyltransferase (MGMT).[130,135] Alisertib, an oral selective inhibitor of aurora kinase A, yielded a partial response rate of 21% (10/48) in patients with high aurora kinase A levels who had previously received treatment for SCLC.[136] A phase 2 randomized trial is currently ongoing comparing alisertib/weekly paclitaxel versus weekly paclitaxel alone. Immune checkpoint inhibitors (eg, ipilimumab, nivolumab) are also being investigated for patients with SCLC.

A randomized phase III trial compared single-agent intravenous topotecan with the combination regimen CAV.[137] Both arms had similar response rates and survival, but intravenous topotecan caused less toxicity. In another phase III trial, oral topotecan improved overall survival when compared with best supportive care (26 vs. 14 weeks).[138] Single-agent topotecan is approved by the FDA as subsequent therapy for patients with SCLC who experience initial response to chemotherapy but then experience progression after 2 to 3 months. In the algorithm, topotecan is recommended as a subsequent agent for patients with relapsed SCLC (category 1 for relapse >2–3 months for up to 6 months; category 2A for relapse <2–3 months).[131,137,139] Either oral or intravenous topotecan may be used, because efficacy and toxicity seem to be similar with either route.[138,139]

Outcomes of Platinum-Sensitive Small-Cell Lung Cancer Patients Treated With Platinum/Etoposide Rechallenge: A Multi-Institutional Retrospective Analysis

Giovenzio Genestreti,[1] Marcello Tiseo,[2] Hirotsugu Kenmotsu,[3] Wakuda Kazushige,[3] Monica Di Battista,[1] Giovanna Cavallo,[1] Federica Carloni,[4] Alberto Bongiovanni,[5] Marco Angelo Burgio,[5] Claudia Casanova,[6] Giulio Metro,[7] Emanuela Scarpi,[8] Taner Korkmaz,[9] Seber Selcuk,[10] Kurup Roopa,[11] Raffaele Califano[11]

Abstract

Small-cell lung cancer has a high chemotherapeutic sensitivity but with disappointing outcome results. Patients with "sensitive disease" are those who respond to treatment with a long relapse-free interval (RFI): in these cases rechallenge with first-line chemotherapy might represent a therapeutic opportunity. Our largest retrospective experience confirmed that rechallenge is feasible with interesting outcome results; there are no statistical differences between RFI and outcome.

Introduction: Patients with small-cell lung cancer (SCLC) that progresses after first-line (FL) chemotherapy have a poor prognosis and second-line (SL) chemotherapy has limited efficacy. Patients whose disease relapses/progresses > 90 days after FL platinum-based treatment are considered platinum-sensitive and could be rechallenged with a similar

Genestreti et al Clinical Lung Cancer 2015

7 Institutions : Italy, UK, Turkey, Japan

Jan 2007- Dec 2011

Retrospective Pharmacy database search

Platinum sensitive (RFI > 90 Days), re-challenged with platinum regimen.

Table 1 Patient Characteristics (n = 2000)

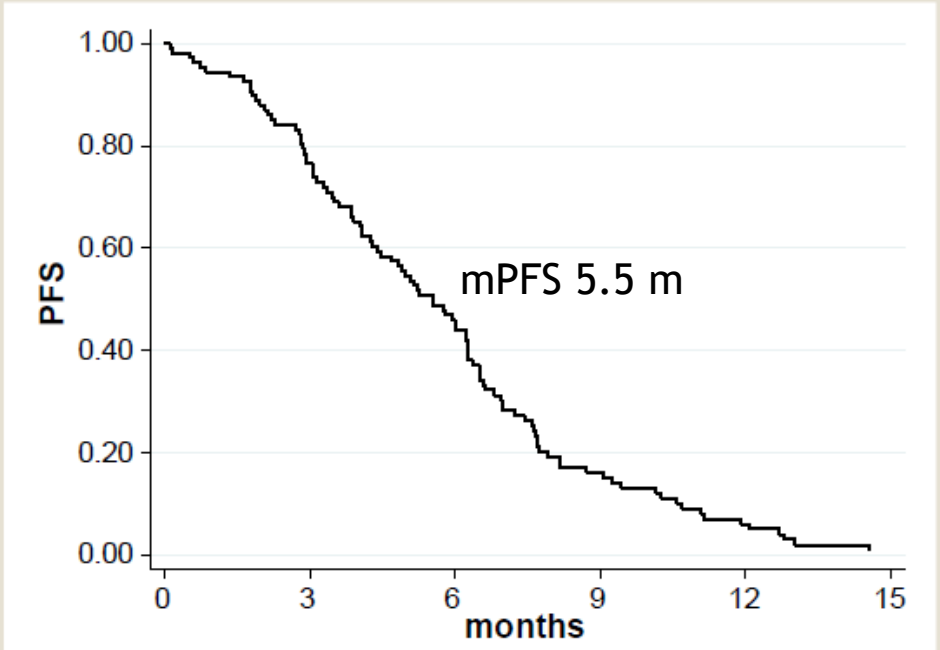
Characteristic	Value
Patients Analyzed	112 (5.6)
Smoking History	
Current smoker	47 (42)
Former smoker	59 (53)
Never smoker	6 (5)
Sex	
Female	39 (35)
Male	73 (65)
Median Age (Range), Years	64 (40-83)
Stage at Time of Diagnosis	
Limited disease	49 (44)
Extensive disease	63 (56)
Performance Score at Time of Diagnosis	
0-1	97 (87)
2	15 (13)
First-Line Chemotherapy Regimen	
Carboplatin and etoposide	51 (46)
Cisplatin and etoposide	61 (54)
Median Courses of First-Line Chemotherapy (Range)	5 (1-6)

Data are presented as n (%) except where otherwise noted, and values are calculated according to the 112 analyzed patients.

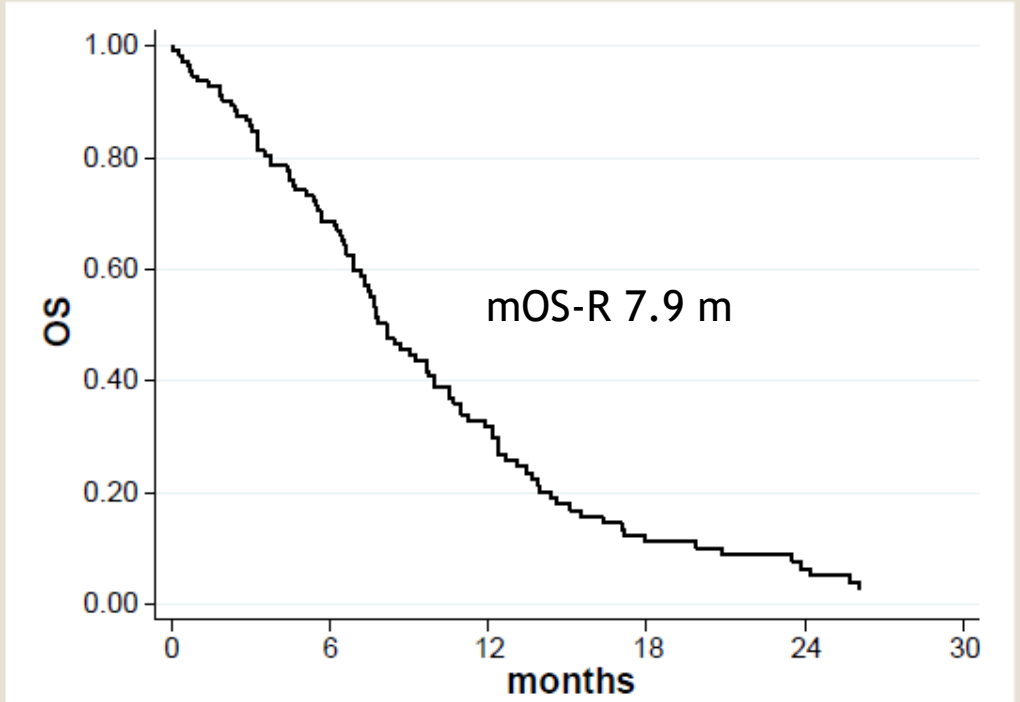
	CR	PR	SD	PD
Response to Re-challenge	3%	42%	19%	27%

Genestreti et al Clinical Lung Cancer 2015

Figure 1 Progression-Free Survival (PFS) From the Time of Starting Rechallenge Therapy



Rechallenge Therapy



Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Outcomes of small-cell lung cancer patients treated with second-line chemotherapy: A multi-institutional retrospective analysis

Marina Chiara Garassino[a,1], Valter Torri[b,1], Giovanni Michetti[c,1], Monica Lo Dico[d,1], Nicla La Verde[a,1], Stefania Aglione[e,1], Andrea Mancuso[f,1], Elisa Gallerani[g,1], Domenico Galetta[h,1], Olga Martelli[i,1], Elena Collovà[j,1], Sonia Fatigoni[k,1], Antonio Ghidini[l,1], Chiara Saggia[m,1], Claudia Bareggi[n,1], Antonio Rossi[o,1], Gabriella Farina[a,1], Nicholas Thatcher[p,1], Fiona Blackhall[p,1], Paul Lorigan[p,1], Raffaele Califano[p,*,1]

Sensitive disease: RFI at least 3 months (N=161)

Table 1
Main patients characteristics.

Main characteristics	No.	%
Sex		
Female	35	22.2
Male	123	77.8
Age (years)		
Median	63	
Range	25–86	
Stage		
Extensive	89	56.3
Limited	69	43.7
ECOG-PS (diagnosis)		
0	56	42.1
1	66	49.6
2	11	8.3
ECOG-PS (at second line)		
0	9	12.5
1	45	62.5
2	18	25
Platinum sensitivity		
Sensitive	121	75.2
Resistant	29	18
Refractory	3	1.8
Unknown	8	5
Type of second line		
Platinum-based rechallenge	30	18.6
VAC or VEC	72	44.8
Topotecan	35	21.7
Other single agents	24	14.9
Brain radiotherapy		
Performed	123	77.8
Not performed	35	22.2
Prophylactic	98	79.6
Palliative	25	20.4

VAC: vincristine, adriamycin and cyclofosfamide; VEC: vincristine, epirubicin and

	Second Line All Patients	Platinum Re-Challenge	Other	P-value
N	161	30 (40% Plat R/R)	131 (21% Plat R/R)	
ORR	22%	34.5%	17.5%	0.06
mPFS	4.3 m	NR	NR	
mOS	5.8 m	9.2 m	5.8 m	0.08

Table 4 Evaluated drugs in relapsed SCLC

						Results		
Drug	**Dose/schedule**	**Authors**	**Population**	**Phase**	**Patients (*n*)**	**Response (%)**	**OS**	**Conclusion**
Gemcitabine	1250 mg m^{-2} days 1, 8; q3w	Hoang *et al* (2003)	Se, Rs, Re	II	27	No response	6.4 months	Limited activity
	1000 mg m^{-2} days 1, 8, 15; q4w	van der Lee *et al* (2001)	Rs, Re (76% >1 earlier line)	II	41	13%	17 weeks	Modest activity
	1000 mg m^{-2} days 1, 8, 15 q4w	Masters *et al* (2003)	Se, Rs, Re	II	46	11.9%	7.1 months	Modest activity
Irinotecan	100 mg m^{-2} weekly	Masuda *et al* (1992)	Se, Rs, Re	II	16	47%	6.8 months	Active agent
Paclitaxel	175 mg m^{-2}; q3w	Smit *et al* (1998)	Rs	II	24	29%	100 days	Active agent
	200 mg m^{-2}; q3w	Joos *et al* (2004)	Rs, Re	II	44	20%	4 months	Active agent
Vinorelbine	25 mg m^{-2} weekly	Furuse *et al* (1996)	Se, Rs, Re	II	24	12.5%	—	Modest activity
	30 mg m^{-2} weekly	Jassem *et al* (1993)	Se	II	26	16%	—	Modest activity
Pemetrexed	500 mg m^{-2}; q3w	Hanna *et al* (2006b)	Se, Rs	II	43	Se: 1 PR Rs: 1 PR	—	Minimal activity
	900 mg m^{-2}; q3w	Gronberg *et al* (2008)	Se, Rs	II	34	Se: 4.5% Rs: 2.9%	17.6 weeks	Limited activity
	900 mg m^{-2}; q3w	Socinski *et al* (2008)	Se, Rs	II	121	0.9% (1 PR in Se)	2.5–6.1 months	Minimal activity
Amrubicin	40 mg m^{-2} days 1–3; q3w	Onoda *et al* (2006)	Se, Rs	II	60	Se OR: 52% Rs OR: 50%	Se: 11.6 months Rs: 10.3 months	Significant activity
	45 mg m^{-2} days 1–3; q3w	Kato *et al* (2006)	Se, Rs	II	35	Se OR: 50% Rs OR: 60%	8.8 months	Significant activity
	40 mg m^{-2} days 1–3; q3w	Kudoh *et al* (2006)	Se, Rs	II	19	OR: 37%	—	Active agent
	40 mg m^{-2} days 1–3; q3w	Ettinger *et al* (2008)	Rs, Re	II	63	PR: 13/39	—	Active agent
	Amrubicin: 40 mg m^{-2} days 1–3; q3w Topotecan: 1 mg m^{-2} days 1–5	Inoue *et al* (2008)	Se, Rs	II	60	38% *vs* 13%	—	Amrubicin may be superior to topotecan
Picoplatin	150 mg m^{-2}; q3w	Bentzion *et al* (2007)	Se, Rs, Re	II	77	—	28.1 weeks	Compares favourably wit other therapeutic options

Abbreviations: OS = overall survival; Se = sensitive (initially responded and then relapsed/progressed between 60 and 180 days); Rs = resistant (initially responded to first-lin

British Journal of Cancer (2010) 102(4), 629 – 638

Original Study

Third-Line Chemotherapy in Small-Cell Lung Cancer: An International Analysis

Demetrios Simos,[1] Golmehr Sajjady,[2] Melissa Sergi,[3] Mun Sem Liew,[4] Raffaele Califano,[5] Cheryl Ho,[6] Natasha Leighl,[7] Shane White,[4] Yvonne Summers,[5] William Petrcich,[8] Paul Wheatley-Price[1]

Clinical Lung Cancer, Vol. 15, No. 2, 110-8

Third-line chemotherapy in SCLC:an international analysis

- Jan 2000 – Dec 2010
- All patients receiving at least 3 lines chemo
- Pure small cell
- Denominator unknown
  - 66/1066 pts (6%) in largest contributing center.

Table 1 Patient Characteristics at Baseline (n = 120)

Characteristic	Value
Treatment Center	
Ottawa	66 (55)
British Columbia	25 (33)
Toronto	15 (13)
Melbourne	7 (6)
Manchester	4 (3)
Median Age at Diagnosis (Range), Years	61 (44-83)
Sex	
Male	70 (58)
Female	50 (42)
Disease Stage at Diagnosis	
Limited	48 (40)
Extensive	72 (60)
ECOG PS at Diagnosis	
0	19 (16)
1	76 (63)
2	16 (13)
3	8 (7)
4	1 (1)
LDH Level at Diagnosis (Unknown in 34)	
Normal	43 (50)
High	43 (50)
Na^+ at Diagnosis (unknown in 6)	
Normal	88 (77)
Low	26 (23)
Hb at Diagnosis (Unknown in 6)	
Normal	102 (89)
Low	12 (11)

- Clinical Lung Cancer, Vol. 15, No. 2, 110-8

D.Simos at all.

Table 2 First-, Second-, and Third-Line Chemotherapy RR and PFS

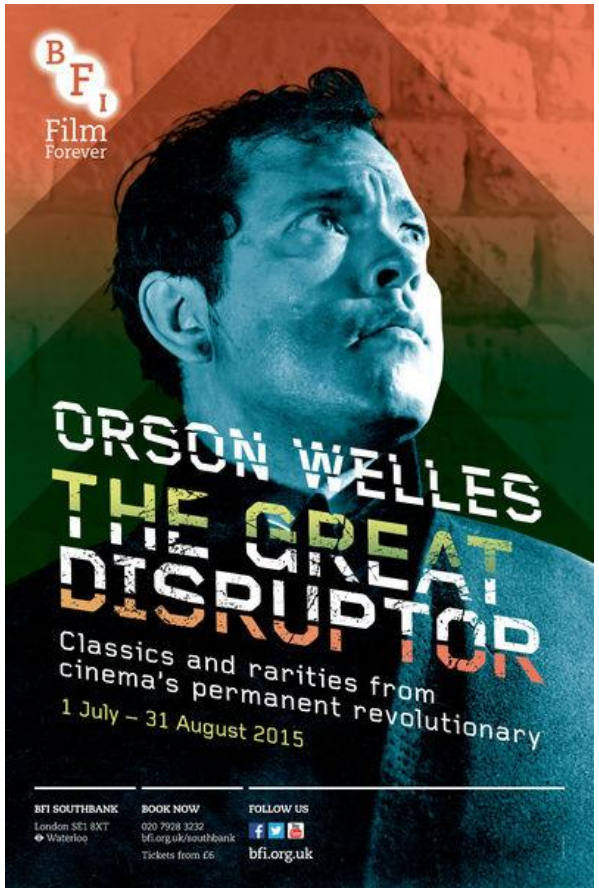
Line of Treatment	Value
First-Line	
Chemotherapy type	
Platinum	119 (99%)
Platinum and etoposide	116 (98%)
Other	1 (1%)
Number Treated in Clinical Trial	8 (7%)
Median Cycles (Range), n	6 (1-6)
Response	
CR and PR	30 + 78 (90%)
SD	7 (6%)
PD	4 (3%)
Not evaluable	1 (1%)
Median PFS (Range), Months	9.0 (1.0-48.6)
Second-Line	
Chemotherapy Type	
Platinum	69 (58%)
Platinum and etoposide	66 (96%)
CAV	31 (26%)
Topotecan	13 (11%)
Other	7 (6%)
Number Treated in Clinical Trial	20 (17%)
Median Cycles (Range), n	4 (1-12)
Response	
CR and PR	4 + 57 (51%)
SD	36 (30%)
PD	23 (19%)
Median PFS (Range), Months	4.6 (0.4-26.3)
Third-Line	
Chemotherapy Type	
Platinum	29 (24%)
Platinum and etoposide	27 (93%)
CAV	52 (43%)
Topotecan	20 (17%)
Other	19 (16%)
Number Treated in Clinical Trial	3 (3%)
Median cycles (Range), n	3 (1-13)
Response	
CR and PR	0 + 21 (18%)
SD	39 (33%)
PD	60 (50%)
Median PFS (Range), Months	2.0 (0.2-15.8)
Median OS (Range), Months	4.7 (0.3-27.5)

22% had 3 distinct treatment regimens

6% had platin based chemo all 3 lines

29% treated b/y 3L

Immunotherapy in Small Cell Lung Cancer



IASLC 2017

IASLC 2017: CheckMate-032: Nivolumab Alone or With Ipilimumab in Recurrent SCLC With High Tumor Mutation Burden

By The ASCO Post

Posted: 10/17/2017 11:22:47 AM

Last Updated: 10/17/2017 5:02:14 PM

Key Points

- Patients with high TMB who received nivolumab plus ipilimumab had an objective response rate of 46%; the objective response rate was 16% and 22% in patients with medium and low levels of TMB, respectively.
- Patients with high TMB who received nivolumab had an objective response rate of 21%; the objective response rate was 7% and 5%, in patients with medium and low levels of TMB, respectively.
- In patients with high TMB who received

At the International Association for the Study of Lung Cancer (IASLC) 18th World Conference on Lung Cancer in Yokohama, Japan, Bristol-Myers Squibb announced data evaluating nivolumab (Opdivo) and nivolumab plus ipilimumab (Yervoy) in previously treated small cell lung cancer (SCLC) patients whose tumors were evaluable for tumor mutation burden (TMB).

Over time, cancer cells accumulate mutations that are not seen in normal cells of the body. Tumor mutation burden is a measurement of the quantity of mutations carried by tumor cells, and is one type of biomarker that may help predict the likelihood a patient responds to immuno-oncology therapies.

CheckMate-032 is an ongoing phase I/II open-label trial

The ASCO Post

ABOUT NEWS MEETINGS TOPICS VIDEOS EARN

FDA Approves Nivolumab for Certain Patients With Previously Treated Small Cell Lung Cancer

By The ASCO Post

Posted: 8/17/2018 12:16:45 PM

Last Updated: 9/14/2018 3:19:32 PM

Today, nivolumab (Opdivo) received approval from the U.S. Food and Drug Administration (FDA) for patients with metastatic small cell lung cancer (SCLC) whose cancer has progressed after platinum-based chemotherapy and at least one other line of therapy. Approval for this indication has been granted under accelerated approval based on overall response rate and duration of response.

This approval for nivolumab had been granted Priority Review from the FDA. It was based on data from the SCLC cohort of the ongoing phase I/II CheckMate-032 study evaluating nivolumab monotherapy in patients who experienced disease progression after platinum-based chemotherapy.

CheckMate-032 Details

Of 109 patients receiving nivolumab after platinum-based chemotherapy and at least one other prior line of therapy, 12% (n = 13/109; 95% confidence interval [CI] = 6.5%–19.5%) responded to treatment based on assessment by a blinded independent central review, regardless of programmed death-ligand 1 (PD-L1) expression. Twelve patients had a partial response (11%), and one patient had a complete response (0.9%). Among these responders, the median duration of response was 17.9 months (95% CI = 7.9–42.1; range = 3.0–42.1 months).

Nivolumab was discontinued in 10% of patients, and 1 dose was withheld in 25% of patients for an adverse reaction. Serious adverse reactions occurred in 45% of patients. The approved dosing for nivolumab in this indication is 240 mg administered every 2 weeks by intravenous infusion until disease progression or

IMpower133: Atezolizumab in Combination With Chemotherapy in Previously Untreated, Extensive-Stage Small Cell Lung Cancer

By The ASCO Post

Posted: 7/3/2018 11:51:46 AM

Last Updated: 9/14/2018 3:35:45 PM

The phase III IMpower133 study recently met its coprimary endpoints of overall survival (OS) and progression-free survival (PFS) at its first interim analysis. The study demonstrated that first-line treatment with the combination of atezolizumab (Tecentriq) plus chemotherapy (carboplatin and etoposide) helped people with extensive-stage small cell lung cancer live significantly longer compared to chemotherapy alone. The atezolizumab-based combination improved progression-free survival (PFS) compared to chemotherapy alone. Safety for the atezolizumab and chemotherapy combination appeared consistent with the known safety profile of the individual medicines, and no new safety signals were identified with the combination. These data will be presented at an upcoming medical meeting.

"These are the first positive phase III survival results for any immunotherapy-based combination in the initial treatment of extensive-stage small cell lung cancer, a particularly difficult-to-treat type of disease," said **Sandra Horning, MD**, Chief Medical Officer and Head of Global Product Development, Genentech. "The clinically meaningful results from the IMpower133 study add to the growing body of evidence demonstrating

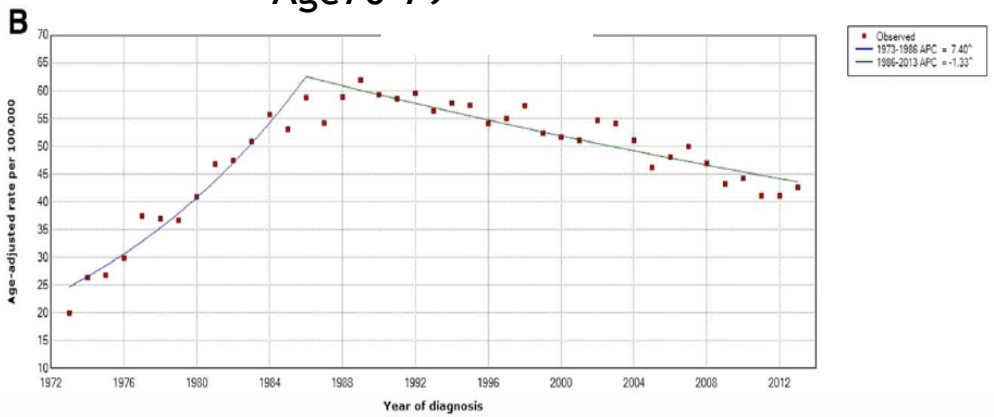
The phase III IMpower133 study recently met its coprimary endpoints of overall survival (OS) and progression-free survival (PFS) at its first interim analysis. The study demonstrated that first-line treatment with the combination of atezolizumab (Tecentriq) plus chemotherapy (carboplatin and etoposide) helped people with extensive-stage small cell lung cancer live significantly longer compared to chemotherapy alone. The atezolizumab-based combination improved progression-free survival (PFS) compared to chemotherapy alone. Safety for the atezolizumab and chemotherapy combination appeared consistent with the known safety profile of the individual medicines, and no new safety signals were identified with the combination. These data will be presented at an upcoming medical meeting.

Treatment of Elderly Patients with Small Cell Lung Cancer

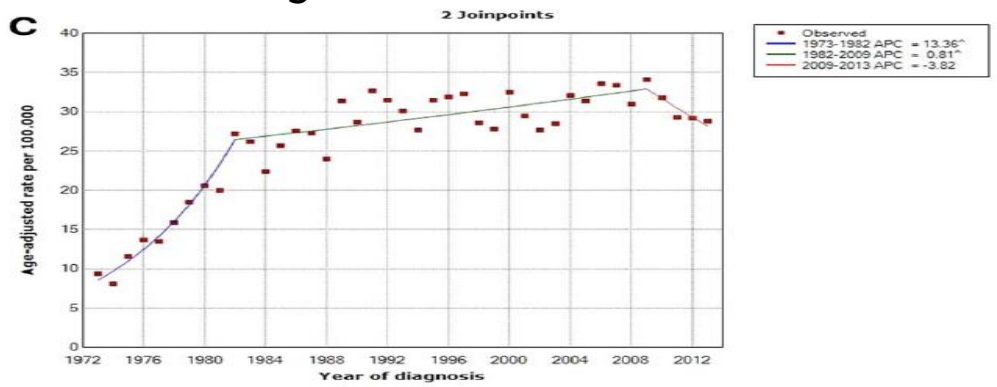
Epidemiology of SCLC in the Elderly

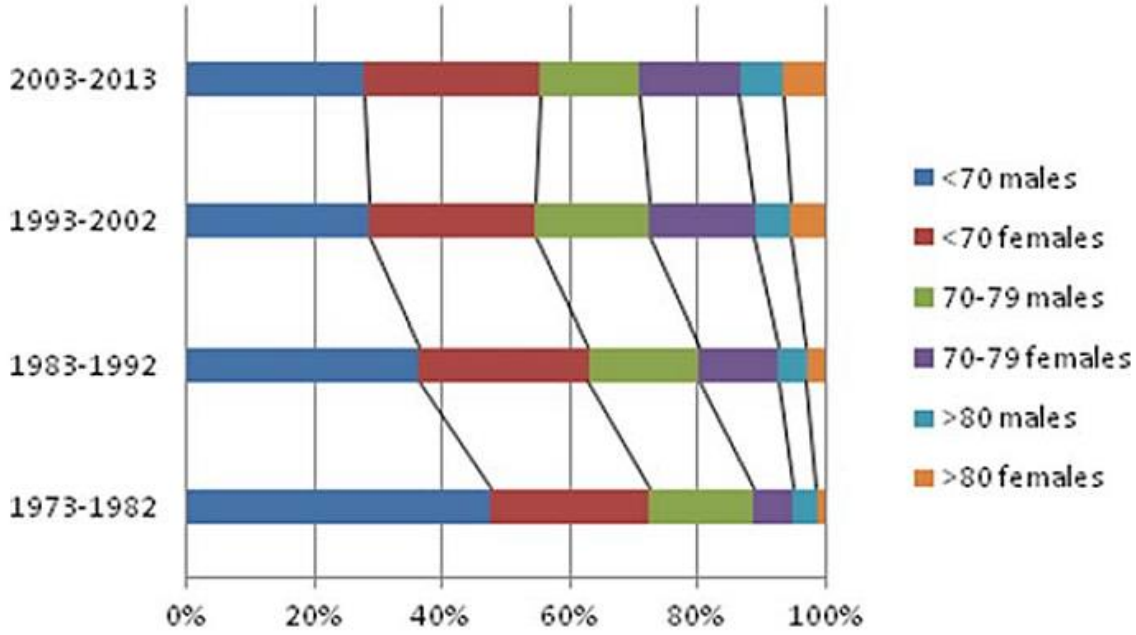
Increasing number of elderly patients with SCLC

Age70-79



Age 80+





Elderly patients (N= 53,664)

23%. 1975

44%. 2010

Abdel-Rahman O. Clin Respir J 2018

SEER Database (1992-2001) N=10428

Factor	Percentage who received chemotherapy, univariate analysis	Odds Ratio, logistic regression	95% Confidence Interval	p-value
Males	67.0%	reference		
Females	67.1%	0.97	0.89-1.06	0.52
Age group				
65 to 69 years	76.1%	reference		
70 to 74 years	71.9%	0.80	0.71-0.90	<0.001
75 to 79 years	63.7%	0.57	0.50-0.64	<0.001
80 to 84 years	50.9%	0.33	0.28-0.38	<0.001
85 years and older	34.7%	0.17	0.14-0.21	<0.001
Comorbidity score				
0	69.1%	reference		
1	66.2%	0.92	0.81-1.06	0.25
2	61.5%	0.77	0.65-0.91	0.003
3	53.0%	0.56	0.45-0.70	<0.001
≥ 4	53.7%	0.57	0.46-0.70	<0.001

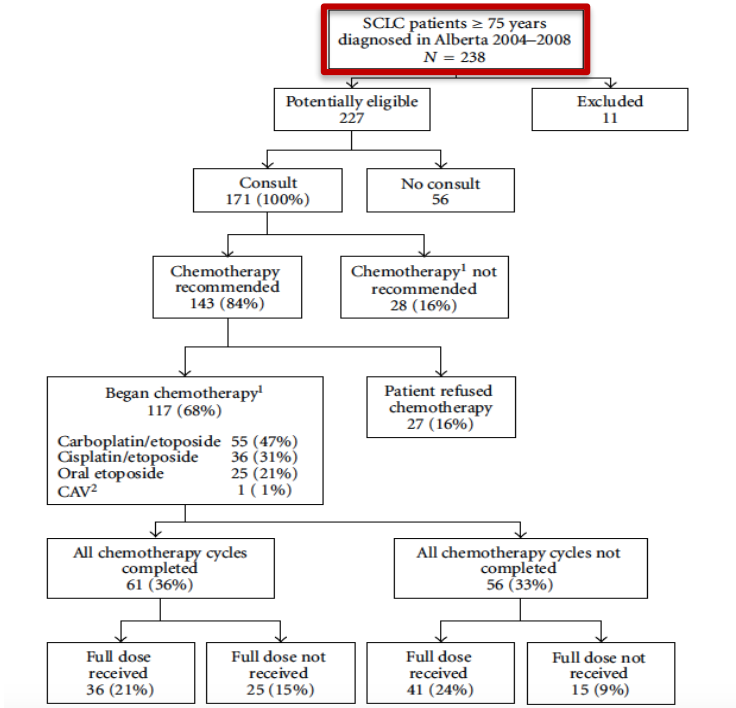
	No Chemotherapy	Chemotherapy	Difference in Survival
All Patients	2.6	9.5	6.9
Males	2.8	9.1	6.3
Females	2.4	10.5	8.1
Age Group			
65 to 69 years	2.8	9.9	7.1
70 to 74 years	2.6	9.9	7.3
75 to 79 years	3.0	9.4	6.4
80 to 84 years	4.8	10.3	5.5
85 years and older	2.9	9.3	6.4

Survival benefit with chemotherapy in all ages

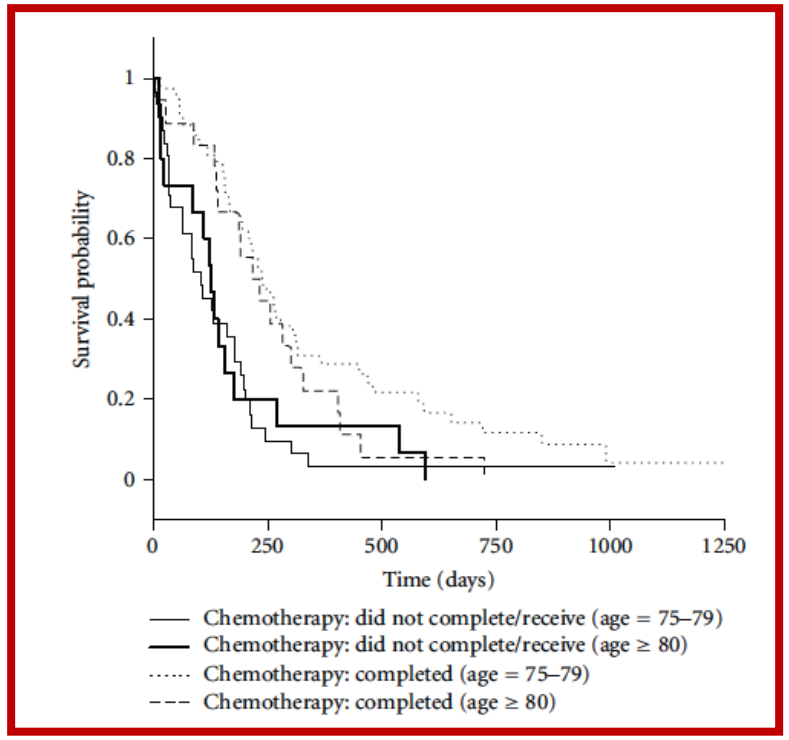
Caprario LC, et al. JTO 2013

What do we know about chemotherapy in the elderly SCLC population?

Retrospective Analyses



52% completed all cycles,
66% did not have any dose reductions



Completing treatment is important

TABLE 6: Adjusted[1] hazard ratio of death of patients 75 years or older diagnosed with SCLC in 2004–2008 in Alberta, Canada, who had an oncologist-consult[2].

	Adjusted[1] hazard ratio (95% CI)	*P* value
ECOG Score		*P* = 0.02
0, 1, and 2	1	
3 and 4	2.01 (1.22, 3.31)	0.007
Missing	1.59 (0.88, 2.88)	0.12
Stage		*P* = 0.33
Limited	1	
Extensive	1.24 (0.80, 1.92)	0.33
Age at diagnosis		*P* = 0.80
75–79	1	
≥80	1.06 (0.66, 1.75)	0.80
Co-morbidities		*P* = 0.05
0 or 1	1	
2 or more	1.63 (1.00, 2.66)	0.05
Drug regimen		*P* = 0.82
Cisplatin/etoposide	1	
Carboplatin/etoposide	1.15 (0.5, 2.65)	0.56
Oral etoposide	1.15 (0.71, 1.89)	0.75
Treatment status		*P* = 0.0018
Complete/full dose	1	
Complete/reduced dose	1.02 (0.57, 1.82)	0.94
Not completed	2.72 (1.52, 4.87)	0.0007
No chemotherapy	2.01 (0.97, 4.18)	0.6

[1]Adjusted for all variables shown in the table.
[2]Start time was 12 weeks after the date of the initial oncologist-consult.

Fisher S et al, Cancer Epidemiology 2012

Geriatric Assessments

Assessment of the Below GA Domains Recommended for All Patients Aged 65+
Function
Falls
Comorbidities
Cognition
Depression
Nutrition

Tools That Can Provide Estimates of Risk for Chemotherapy Toxicity
CARG toxicity tool: 11 items provides estimates for overall risk of grade 3 to 5 chemotherapy toxicity.
CRASH tool: 3 items provides estimates separately for risk of grade 3 hematologic and grade 3 to 4 nonhematologic toxicity

Screening Tools That Have Been Independently Associated with Adverse Outcomes in Older Patients with Cancer Receiving Chemotherapy
GB – 8 items G8 is independently associated with mortality (1 year and 3 years), even when controlling for ECOG PS and stage of cancer
VES-1 – 13 items

Treatment of Patients with Poor Performance Status (ECOG 3-4)

Early metastatization

Two-thirds of cases extensive stage

SVCS 10%

Constitutional symptoms may indicate extrathoracic spread

Hyponatremia may be related to SIADH

Pietanza MC ePietanza MC et al: In: DeVita 2015

SCLC presentation

Symptom or sign	Frequency, %
Local	
Cough	50
Dyspnoea	40
Chest pain	35
Haemoptysis	20
Hoarseness	10
Distant	
Weight loss	50
Weakness	40
Anorexia	30
Paraneoplastic syndromes	15
Fever	10

Table 2: **Frequency of presenting symptoms in small-cell lung cancer**

Panel: **Favourable prognostic factors in patients with small-cell lung cancer[82–86]**

Factors consistently reported

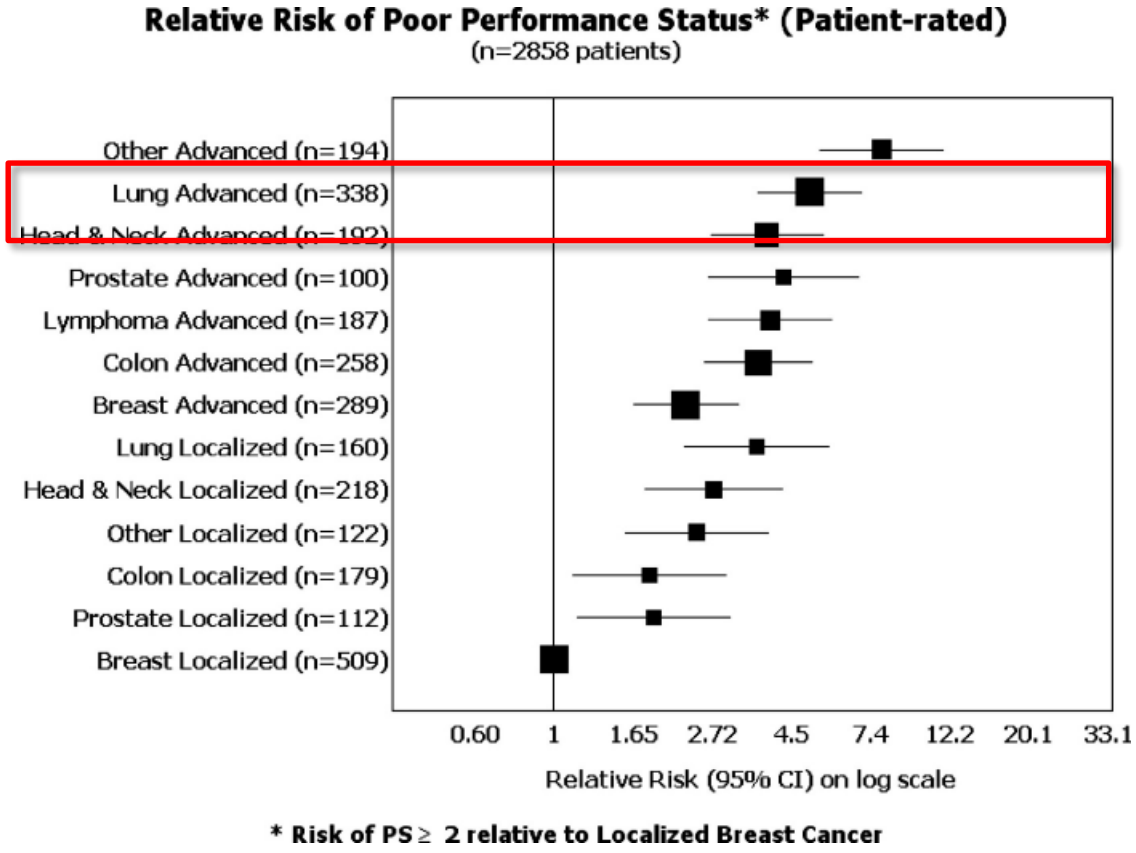
- Good performance status
- Limited-stage disease
- Female sex
- Normal serum lactate dehydrogenase

Factors inconsistently reported

- Few sites of metastatic disease
- Absence of pleural effusion
- Absence of brain metastases
- Absence of liver metastases
- Age <40 years
- Normal serum sodium concentration
- Normal liver-function results

Jackman DM & Johnson BE.
Lancet2005;366:1385-96

Performance Status



- The risk of poor PS was greatest for patients with advanced disease, particularly those with advanced lung cancer
- Half the patients with lung cancer, regardless of stage, rated their PS as poor (49%)
- In SCLC, it has been described that up to 30% of patients may have a PS of 3 or 4

Lilenbaum RC et al. J Thorac Oncol 2008;3(2):125-129. Baldotto CS et al. Support Care Cancer 2007;131:883-895.

Performance Status

Patients with a poor PS are associated with increased risk for chemotherapy toxicity and poor outcomes compared to patients with better PS

Accurate PS scoring is of critical importance because many clinical decisions are based on PS including the planning, randomization, eligibility for and evaluation of clinical trials

PS defines therapy in most solid tumors

PS 0

PS 1

PS 2

PS 3

PS 4

GO

Why are oncologists willing to treat SCLC patients despite poor PS?

- NO

Why are oncologists willing to treat SCLC pts despite poor PS?

GO

High response rate

Symptom relief

Try a couple of cycles

NO

Poor prognosis

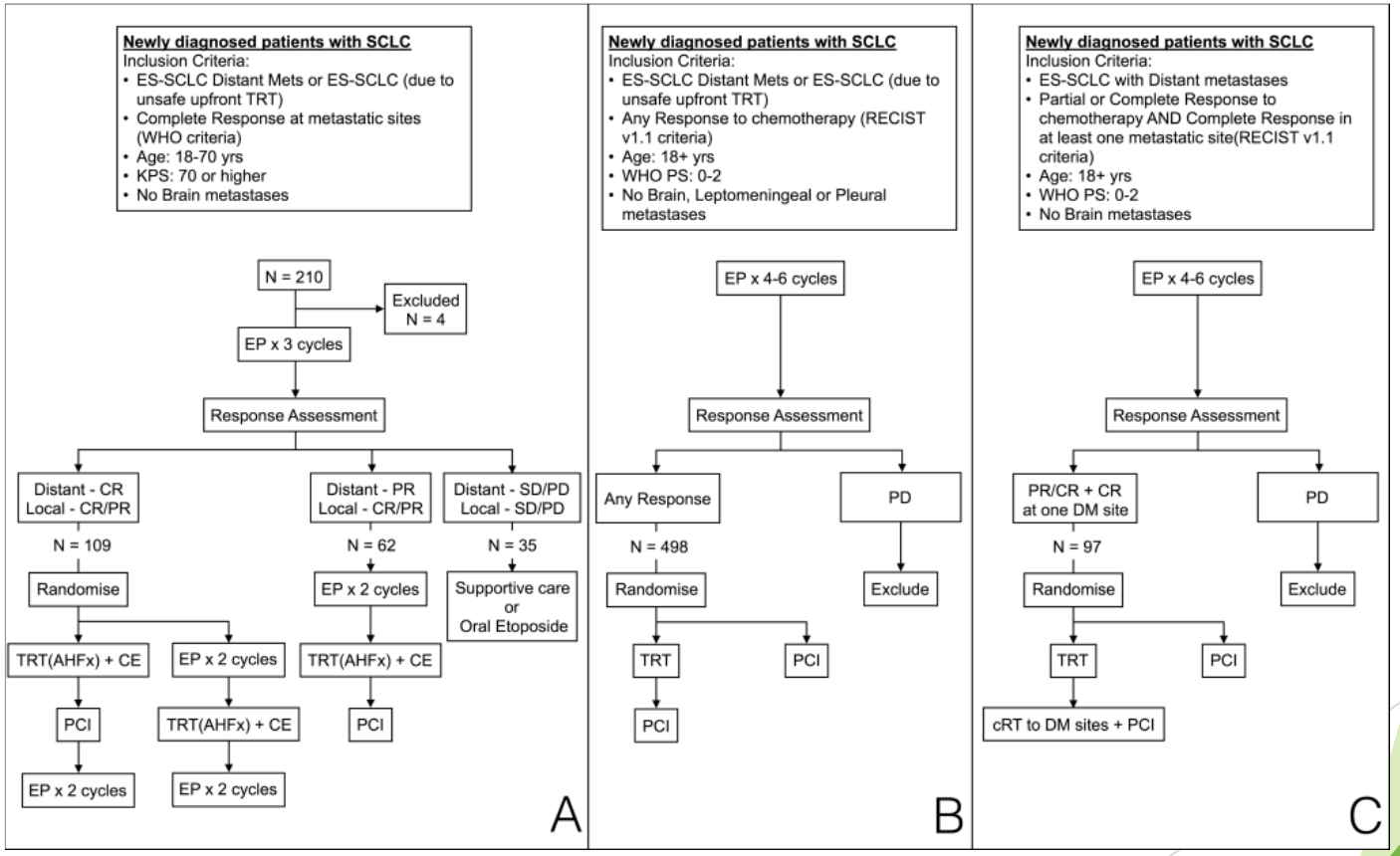
CT toxicity

Expectations

Lilenbaum RC et al. J Thorac Oncol 2008;3(2):125-129. Baldotto CS et al. Support Care Cancer 2007;131:883-895.

Thoracic radiation in ES-SCLC

- KPS ≥ 70%
- CR at metastatic sites



- PS 0-2
- PR or CR

Ahmad I, Chufal K. J Cancer Res Update 2017;6:74-77

Second line and beyond

*The decision for second-line and beyond treatment in relapsed SCLC should take into consideration the **performance status** and comorbidities of the patient, organ reserve, toxicity experienced from previous chemotherapy, response and disease-free interval from prior therapy, and treatment goals.*

Second line and beyond

GO

~~High response rate~~

~~Symptom relief~~

Try a couple of cycles

NO

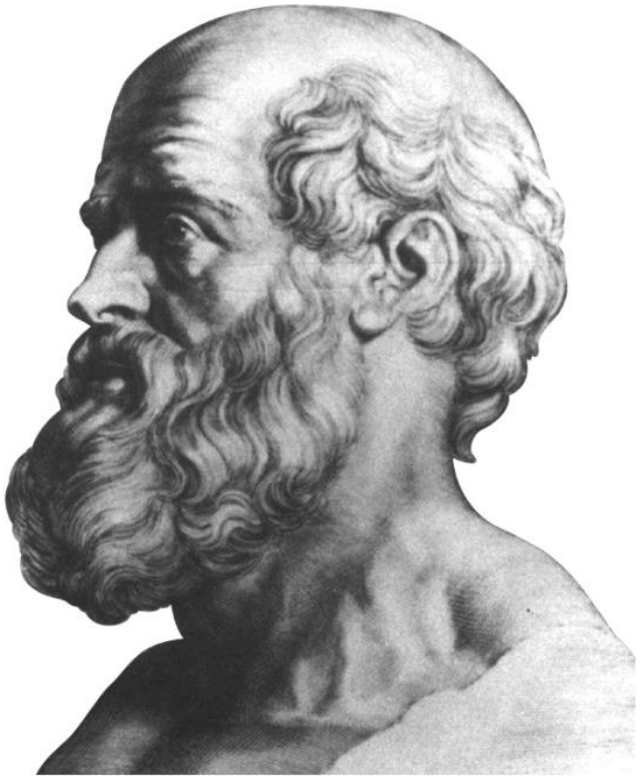
Poor prognosis

CT toxicity

Expectations

Conclusions

- SCLC patients often present with poor PS (underrepresented in trials)
- Very few patients will derive a long-term benefit
- The primary goal is providing symptom relief (survival gain when possible)
- There is a need for clinical trials aiming at poor PS patients



"*To cure sometimes, to relieve often, to comfort always*"

(Hippocrates)