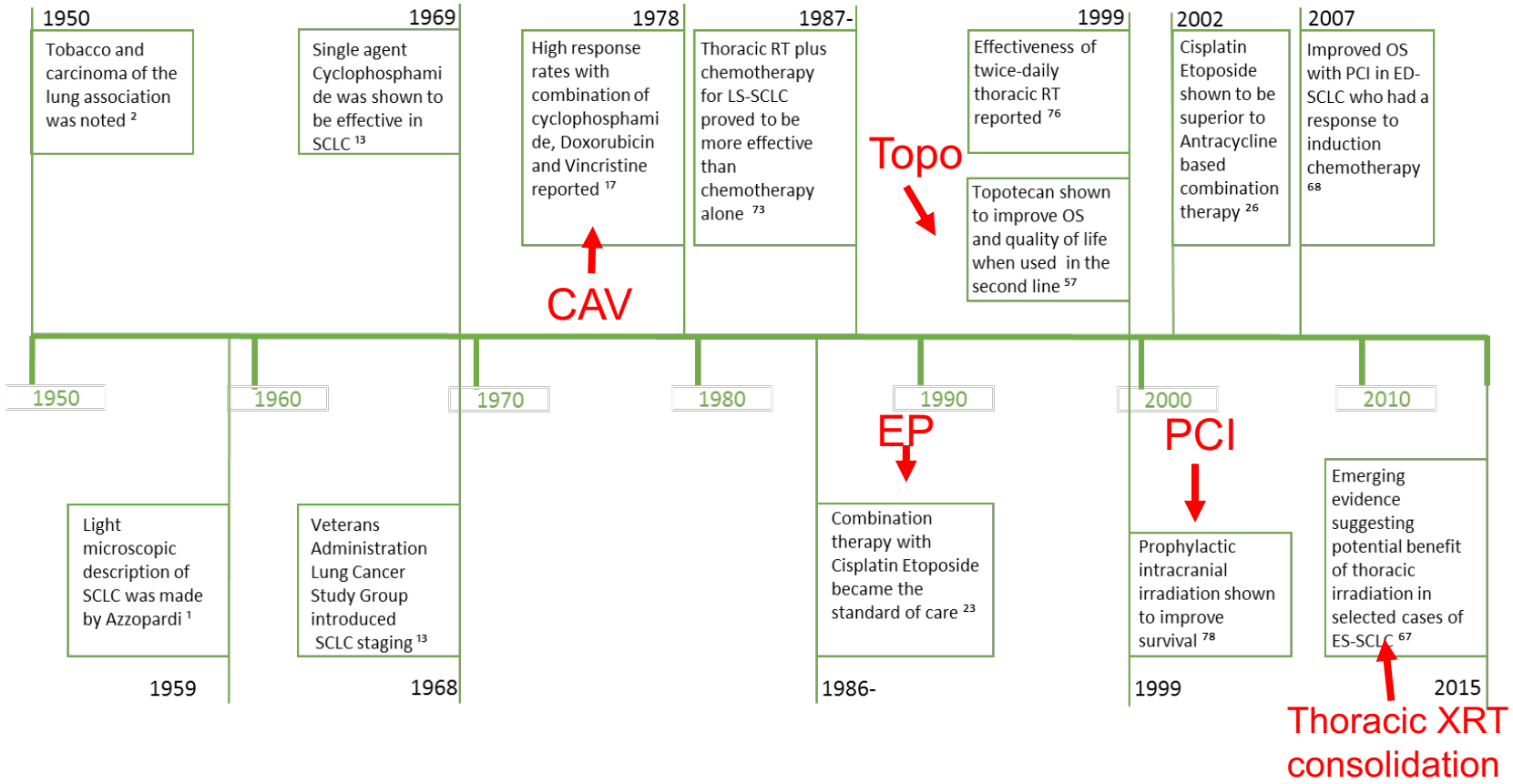
# Small Cell Lung Cancer: 1L and Beyond

Anne Chiang MD PhD
Associate Professor, Division of Thoracic Medical Oncology
Yale University School of Medicine
Associate Cancer Center Director, Clinical Initiatives
Yale Cancer Center

# FROM 1960-2018: MILESTONES in SCLC: CHEMOTHERAPY AND RADIATION APPROACHES




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

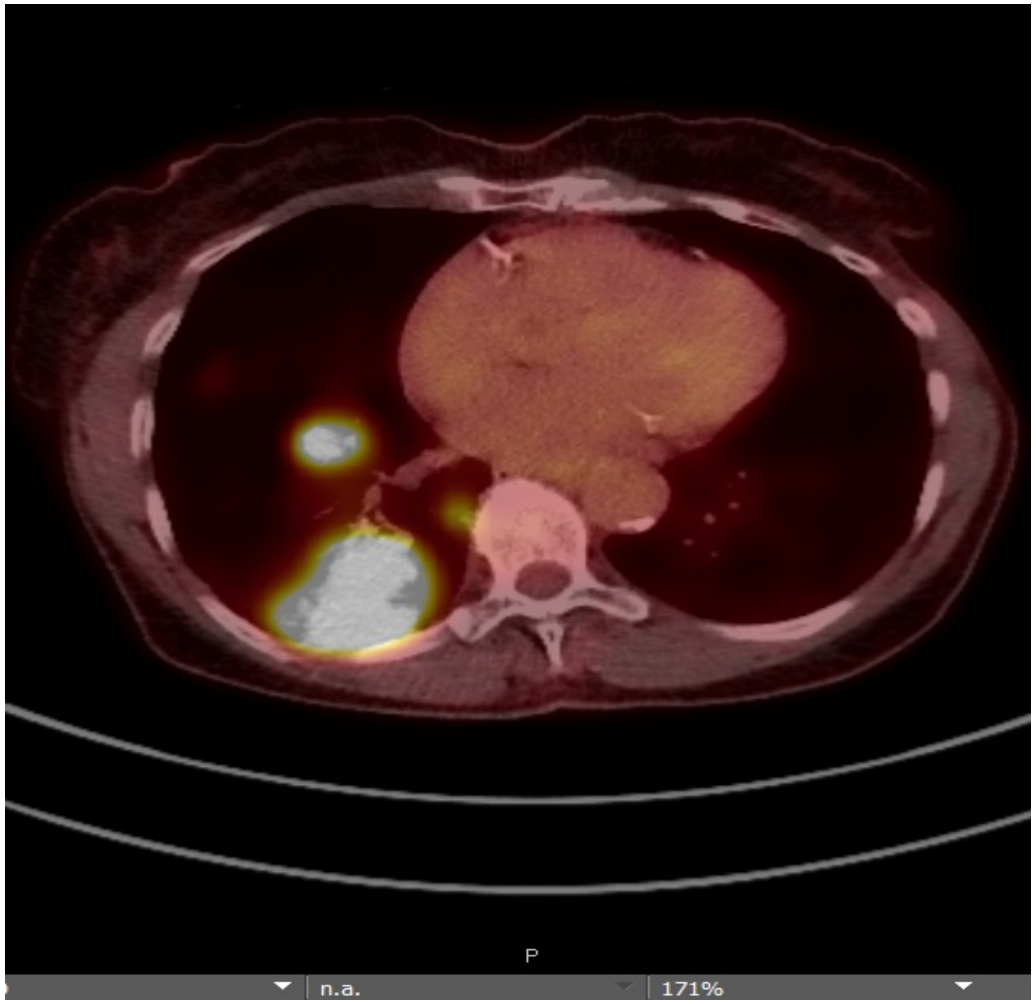


*Altan, Chiang. Cancer J. 2015 Sep-Oct;21(5):425-33*

# Case # 1 Presentation at Diagnosis

- 65-year-old African American female (40 py tobacco history) presented in spring 2020 with weight loss over several months, worsening SOB on exertion, abdominal discomfort
- Physical exam reveals shotty neck adenopathy, right axillary LAD
- PET scan shows 7.2 cm RLL mass, additional tumor nodules in RLL, extensive regional nodal involvement in right hilar, mediastinal, and axillary LNs.
- Brain MRI is negative
- Biopsy of LN reveals small cell carcinoma,  positive for synaptophysin, Ki-67 is 90%

How would you treat this patient?



# Case # 1

## All are correct

- What regimen do you use?

a. Carbo/etoposide
b. Carbo/etoposide/atezolizumab
c. Carbo/etoposide/durvalumab
d. Cis/etoposide/durvalumab

| PRIMARY THERAPY FOR EXTENSIVE-STAGE SCLC: |
|---|
| Four cycles of therapy are recommended, but some patients may receive up to 6 cycles based on |
| **Preferred Regimens** |
| • Carboplatin AUC 5 day 1 and etoposide 100 mg/m² days 1, 2, 3 and atezolizumab 1,200 mg day 1 e 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 e 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 da 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 c 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] |

carbo = carboplatin; cis = cisplatin; WBRT = whole-brain radiotherapy.

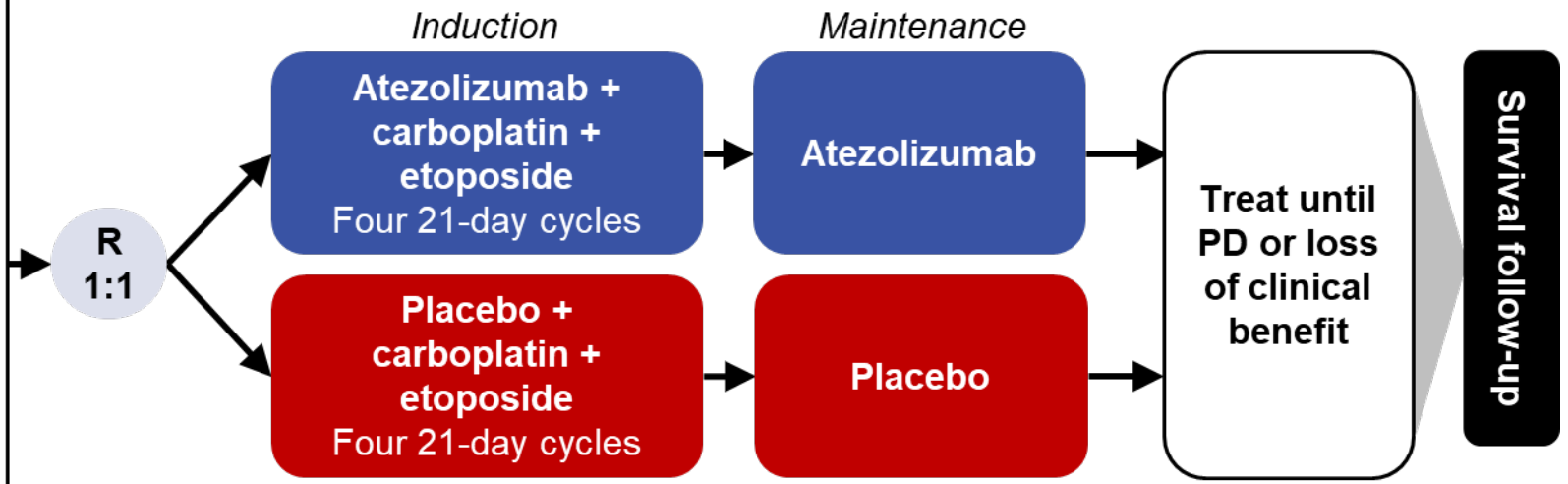
# IMpower133: Atezolizumab/Carboplatin/Etoposide

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

**Stratification**

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

**N=403**

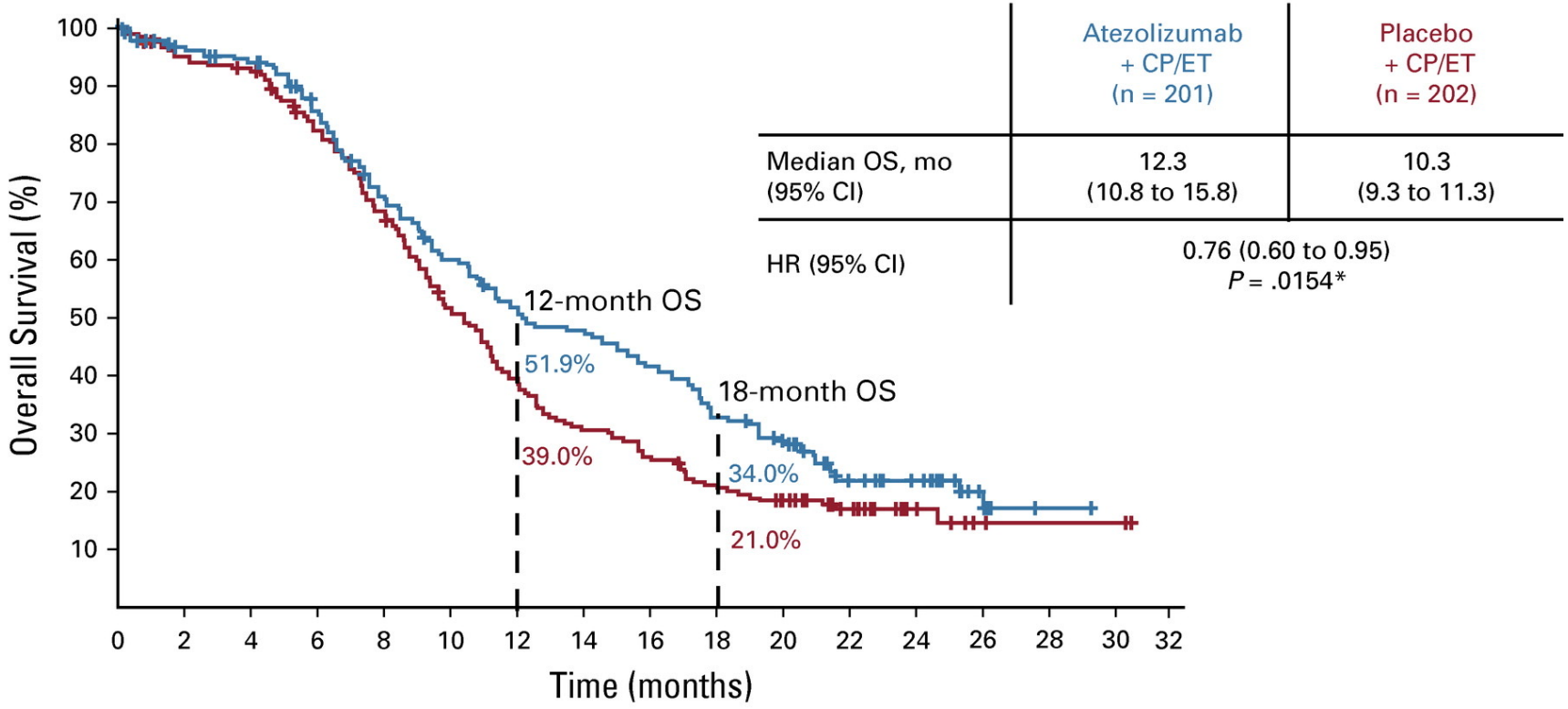



**Primary endpoints**

- ✓ OS
- ✓ Investigator-assessed PFS

# IMpower133: Atezolizumab/Carboplatin/Etoposide

**A**




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

No. of Patients at Risk

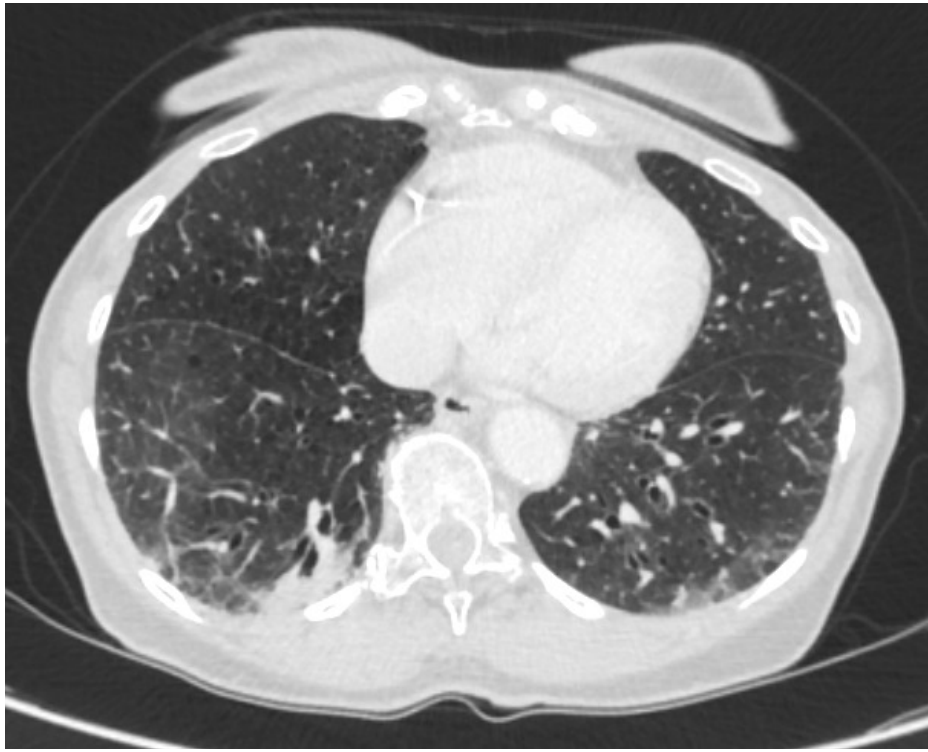
| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Atezolizumab + CP/ET | 201 | 187 | 180 | 159 | 130 | 109 | 93 | 86 | 75 | 61 | 51 | 28 | 21 | 8 | 1 |
| Placebo + CP/ET | 202 | 189 | 183 | 160 | 131 | 97 | 74 | 58 | 49 | 39 | 33 | 20 | 8 | 3 | 2 |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

**Stephen V. Liu; Martin Reck; et al, *Journal of Clinical Oncology* 2021 39619-630**. Median Follow up 22.9 months

# Case # 1-cont

- Pt has excellent response to 4 cycles of carboplatin, etoposide and atezolizumab and continues maintenance on monthly atezolizumab
- Atezo tolerated well except immunotherapy- induced lichenoid rash controlled with steroid topical cream
- Pt is on cycle 9 of maintenance Atezo

How long do you continue maintenance immunotherapy?



# IMpower133: Safety and Adverse Events

**TABLE 1.** Safety Summary and Drug Exposure

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

<u>Atezo vs Placebo Arms</u>:

TrAEs
- G3/4: 57.1 vs 56.1%
- G5: 1.5 vs 1.5%
- Atezo or Placebo-related
- G3/4: 57 vs 56%
- G5: 1.5 vs 1.5%

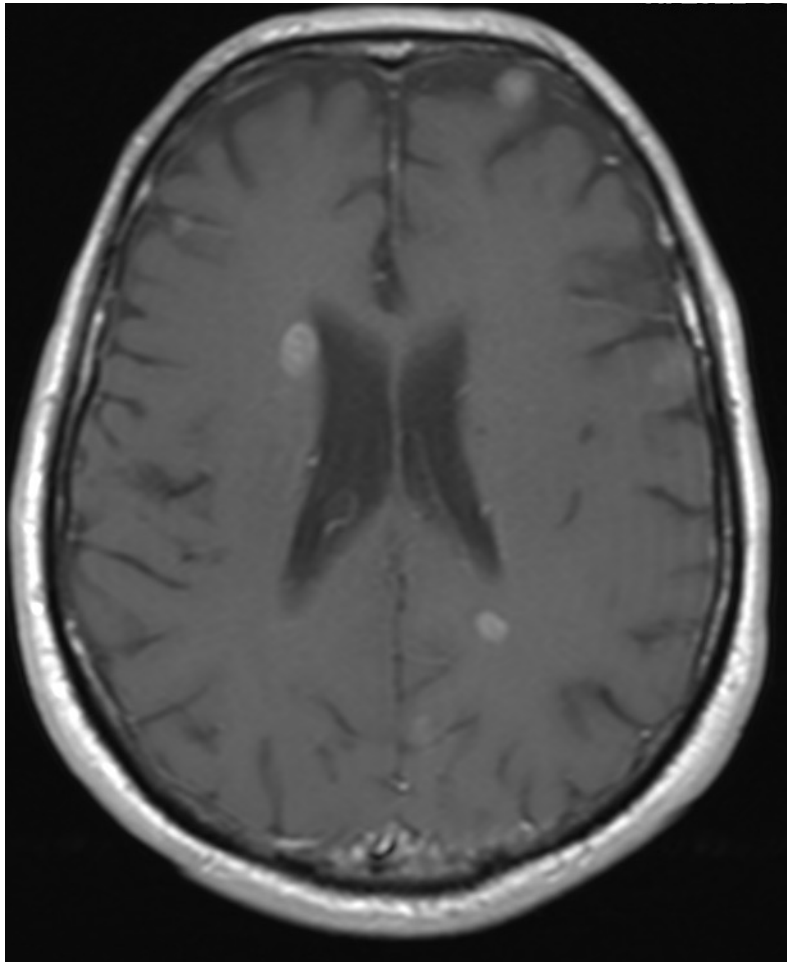
Maintenance Atezo treatment duration, median:
- 4.7 vs 4.1 mo

Total cumulative atezo dose:
- 8,400 mg (7 doses) vs 0

# Case # 2

- 67-year-old white male (50 py tobacco history) presented in spring 2021 with weight loss over several months, dysphagia, worsening SOB on exertion, weakness
- CT scan shows 6.2x 3.6 cm mediastinal mass extending into the SVC/RUL bronchus, bulky right hilar mass, multiple satellite solid nodules throughout the right lung
- Brain MRI shows numerous subcentimeter supra- and infratentorial lesions
- EBUS/Biopsy of RUL lung, 4R and 4L LN reveals small cell carcinoma,  positive for TTF1, INSM1

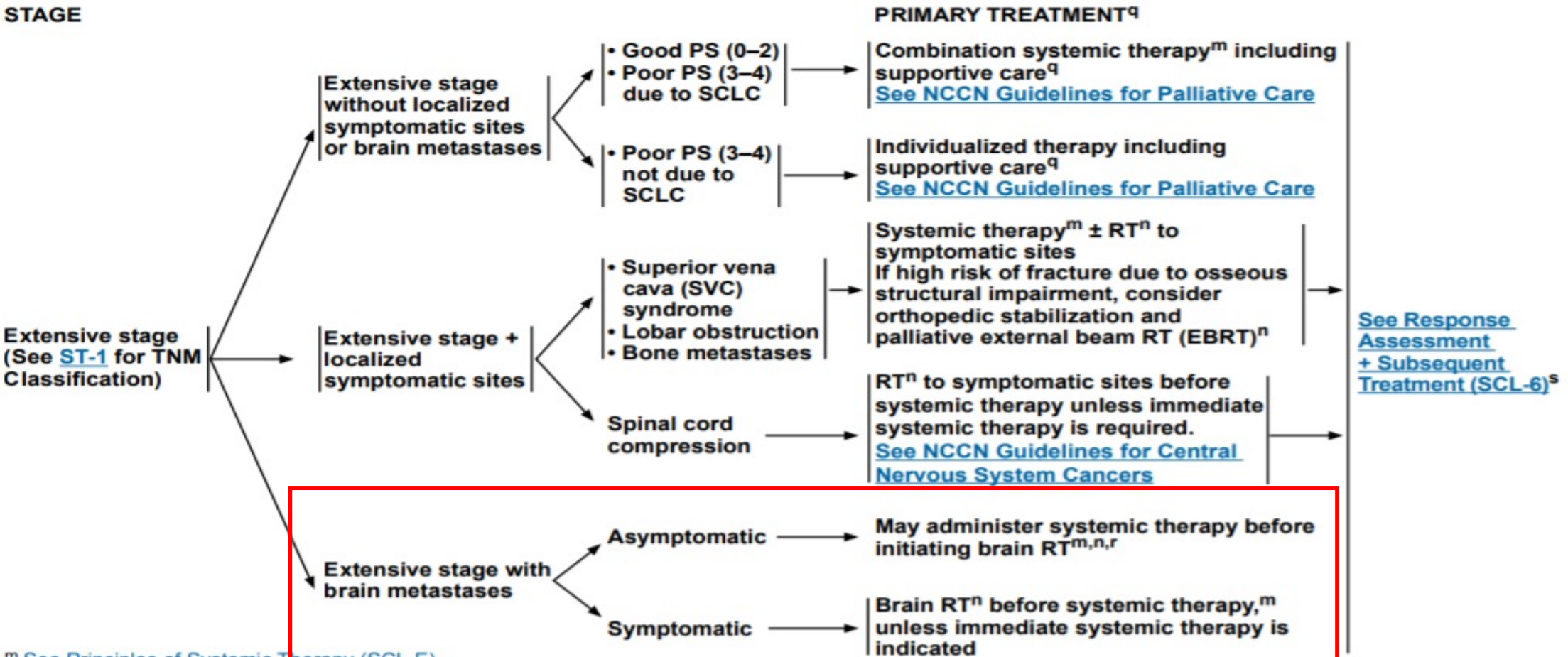
What is the next step in treatment?



National Comprehensive Cancer Network®

# NCCN Guidelines Version 1.2022
# Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion




[m] See Principles of Systemic Therapy (SCL-E).
[n] See Principles of Radiation Therapy (SCL-F).
[q] See Principles of Supportive Care (SCL-D).
[r] Brain MRI (preferred) or CT with contrast should be repeated after every 2 cycles of systemic therapy until brain RT is initiated or systemic therapy is completed, whichever is first (see SCL-6). If brain metastases progress while on systemic therapy, brain RT should be initiated before completion of systemic therapy. See Principles of Radiation Therapy (SCL-F).
[s] During systemic therapy, response assessment by chest/abdomen/pelvis CT with contrast should occur after every 2–3 cycles of systemic therapy and at completion of therapy (SCL-6).

# CASPIAN Study Design

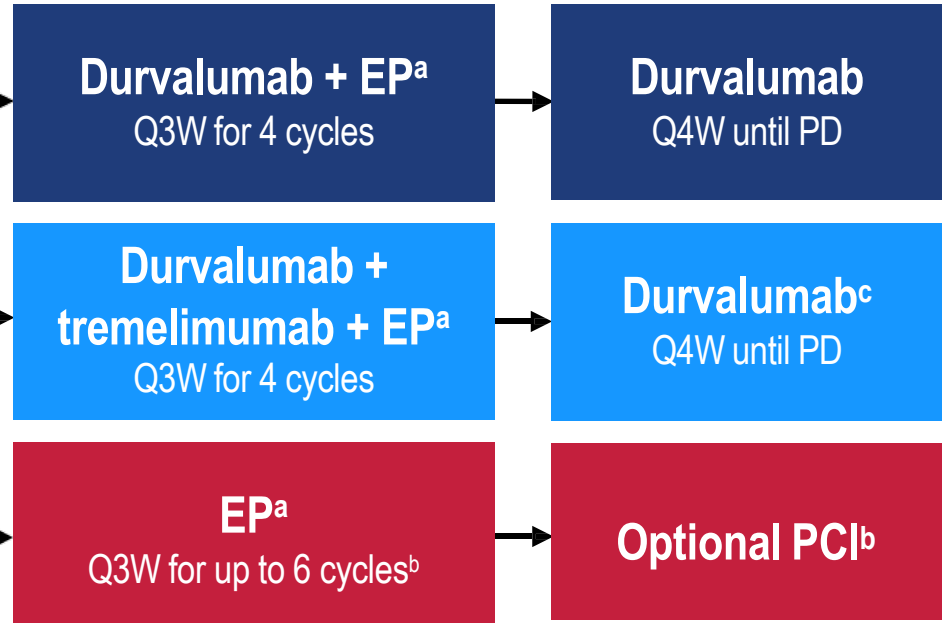
## Phase 3, global, randomized, open-label, active-controlled, multicenter study

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

N=805 (randomized)

1:1:1 R

Stratified by planned platinum (carboplatin vs cisplatin)




**Primary endpoint**

- OS

**Secondary endpoints**

- PFS[d]
- ORR[d]
- Safety & tolerability
- PROs

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

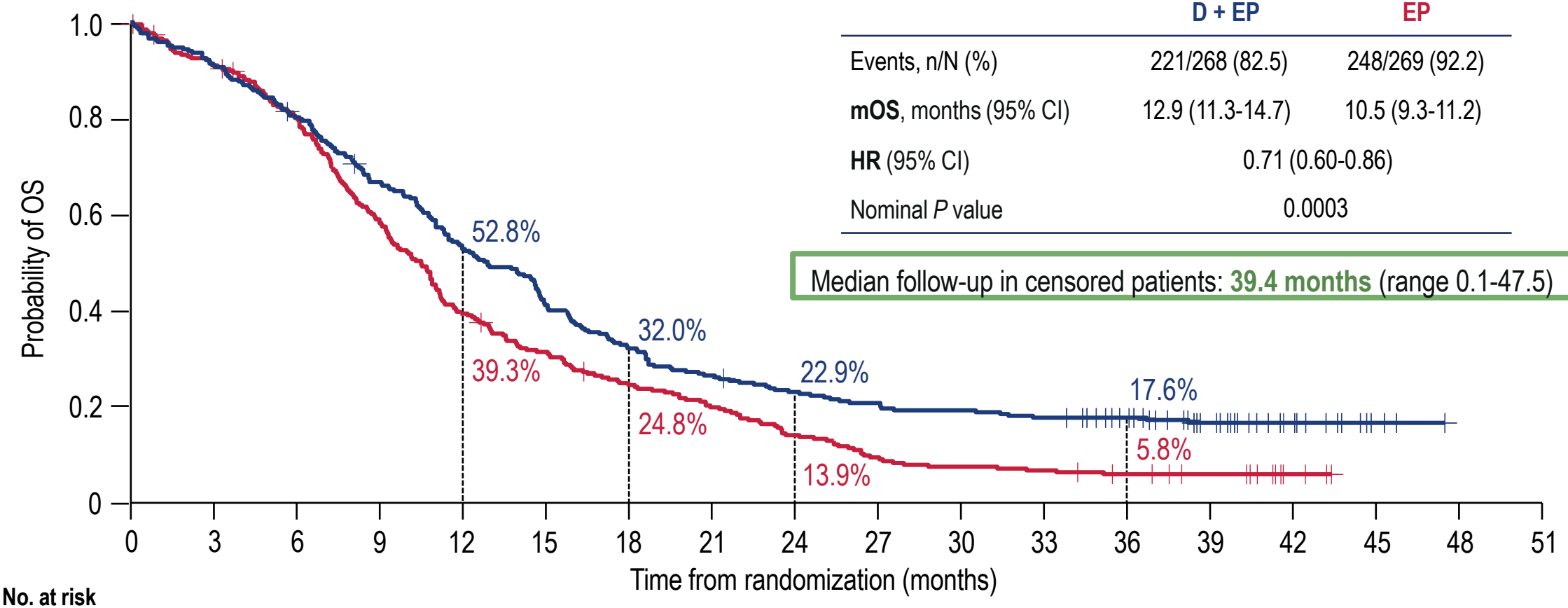
[a]EP consists of etoposide 80-100 mg/m$^2$ with either carboplatin AUC 5-6 or cisplatin 75-80 mg/m$^2$, durvalumab dosed at 1500 mg, tremelimumab dosed at 75 mg. [b]Patients could receive an additional 2 cycles of EP (up to 6 cycles total) and PCI at the investigator's discretion. [c]Patients received an additional dose of tremelimumab post EP.

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

# 3-Year OS Update: D + EP vs EP

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

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




**No. at risk**

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

Data cutoff: March 22, 2021. Paz-Ares LG, et al. *Ann Oncol*. 2021;32(suppl 5):S1283-S1346.

YaleNewHavenHealth Smilow Cancer Hospital | Yale CANCER CENTER A Comprehensive Cancer Center Designated by the National Cancer Institute | Yale SCHOOL OF MEDICINE

# Serious AEs: 3-Year Update

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

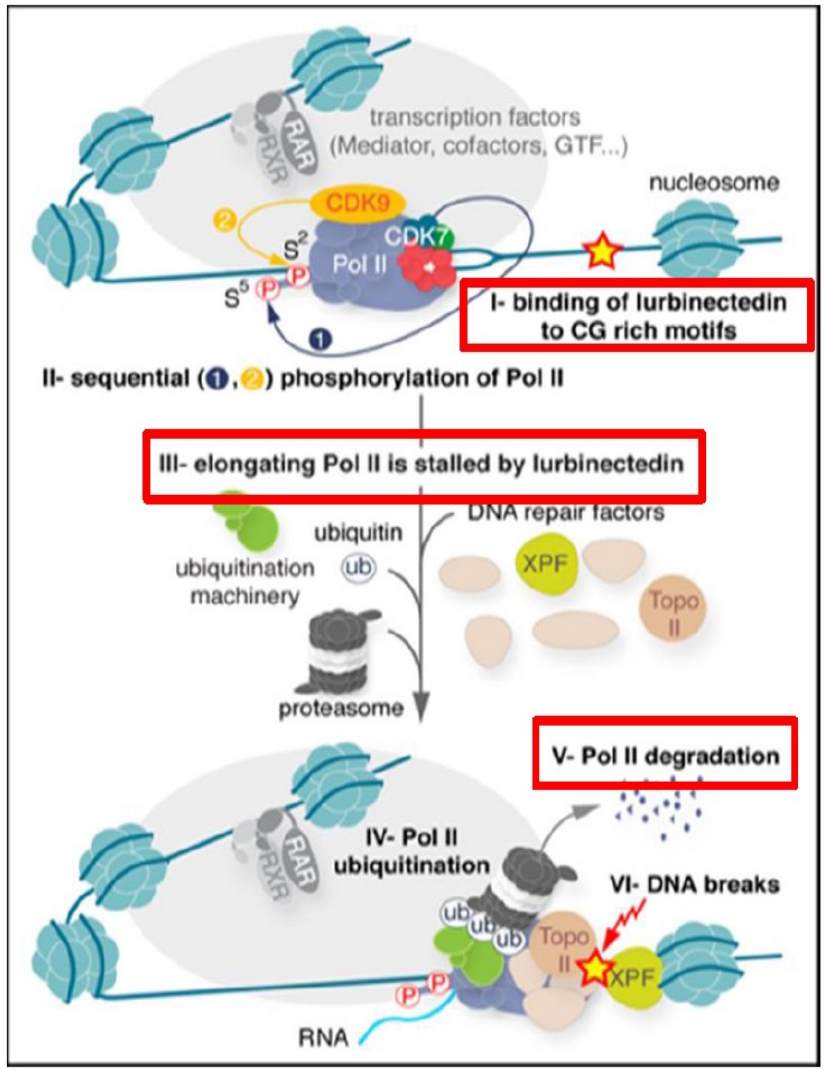
[a]Serious AEs occurring in ≥2% of patients in any treatment arm are shown. [b]Four additional deaths were reported since the previous analysis (none considered treatment related): 1 in the D+EP arm (aspiration), 2 in the D+T+EP arm (drowning and *pneumocystis jirovecii* pneumonia), and 1 in the EP arm (small intestine leiomyosarcoma).

# FDA approvals for 1L ES-SCLC: Updated Analyses

| | IMpower133 updated analysis | CASPIAN updated analysis |
|---|---|---|
| Median follow up | 22.9 mo | 39.4 mo |
| mOS | 12.3 vs 10.3 mo | 12.9 vs 10.5 mon |
| HR | 0.76, p=0.0154 | 0.71, p=0.0003 |
| 1YOS | 51.9 vs 39% | 52.8 vs 39.3% |
| 2YOS | 22 vs 17% | 22.9 vs 13.9% |
| 3YOS | | 17.6 vs 5.8% |
| Eligibility | Treated brain mets only | Asymptomatic brain mets allowed |
| Chemo | Carboplatin | Cis or carboplatin |
| New Technology Add-on Payments (NTAP) | yes | yes |

# Lurbinectedin

- Lurbinectedin binds to the minor groove of DNA
- Mechanisms of action:
  - inhibits transcription through stalling and degradation of RNA polymerase II
  - induces DNA double-strand breaks resulting in apoptosis



# Phase II Lurbinectedin in Relapsed SCLC

- Relapse after only 1 prior regimen, no CNS mets, PS 0-2
- Lurbinectedin 3.2 mg/m$^2$ q 3 wk

| | N | Response | | | PFS | | Overall Survival | |
|---|---|---|---|---|---|---|---|---|
| | | ORR | DCR | DOR | Median | 6-Month | Median | 1-Year |
| **All patients** | 105 | **35%** | 69% | 5.3 mo. | 3.5 mo. | 33% | 9.3 mo. | 34% |
| **Resistant** (< 90 days) | 45 | **22%** | 51% | 4.7 mo. | 2.6 mo. | 19% | 5.0 mo. | 16% |
| **Sensitive** (≥ 90 days) | 60 | **45%** | 82% | 6.2 mo. | 4.6 mo. | 44% | 11.9 mo. | 48% |
| ≥ 180 days | 20 | **60%** | 95% | 5.5 mo. | 4.6 mo. | NR | 16.2 mo. | 61% |



*Trigo et al, Lancet Oncol 21:645; Subbiah et al, Lung Cancer 150:90, 2020*

# FDA approvals for Relapsed SCLC

**Lurbinectidin, approved June 2020**

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

**Pembrolizumab, approved June 2019 NOW WITHDRAWN**

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

**Nivolumab, approved Aug 2018 NOW WITHDRAWN**

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

## SCLC SUBSEQUENT SYSTEMIC THERAPY (PS 0–2)[c]
**Consider dose reduction or growth factor support for patients with PS 2.**

**Preferred Regimens**
- Platinum-based doublet[d,e,f,36,37]
- Clinical trial

**Other Recommended Regimens**
- Topotecan oral (PO) or intravenous (IV)[14-16]
- Lurbinectedin[17,38]
- Cyclophosphamide/doxorubicin/vincristine (CAV)[14]
- Docetaxel[20]
- Oral etoposide[24,25]
- Gemcitabine[28,29]
- Irinotecan[21]
- ~~Nivolumab[b,d,30,31]~~
- Paclitaxel[18,19]
- ~~Pembrolizumab[b,d,32-34]~~
- Temozolomide[22,23]
- Vinorelbine[26,27]
- Bendamustine (category 2B)[35]

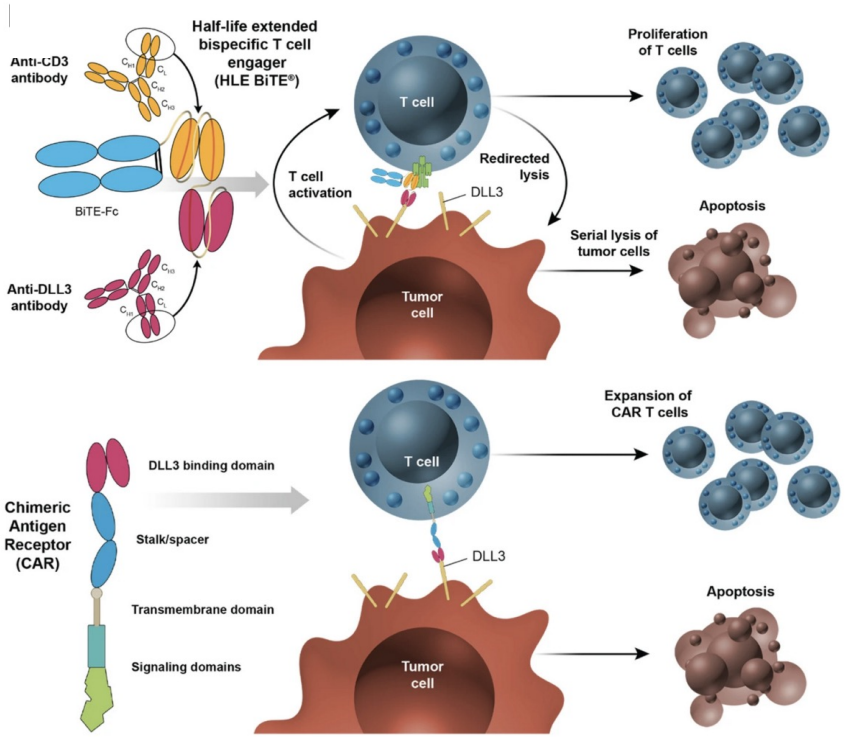
**b** Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or concurrent use of immunosuppressive agents.

**d** The use of immune checkpoint inhibitors is discouraged if there is progression on maintenance atezolizumab or durvalumab at time of relapse.

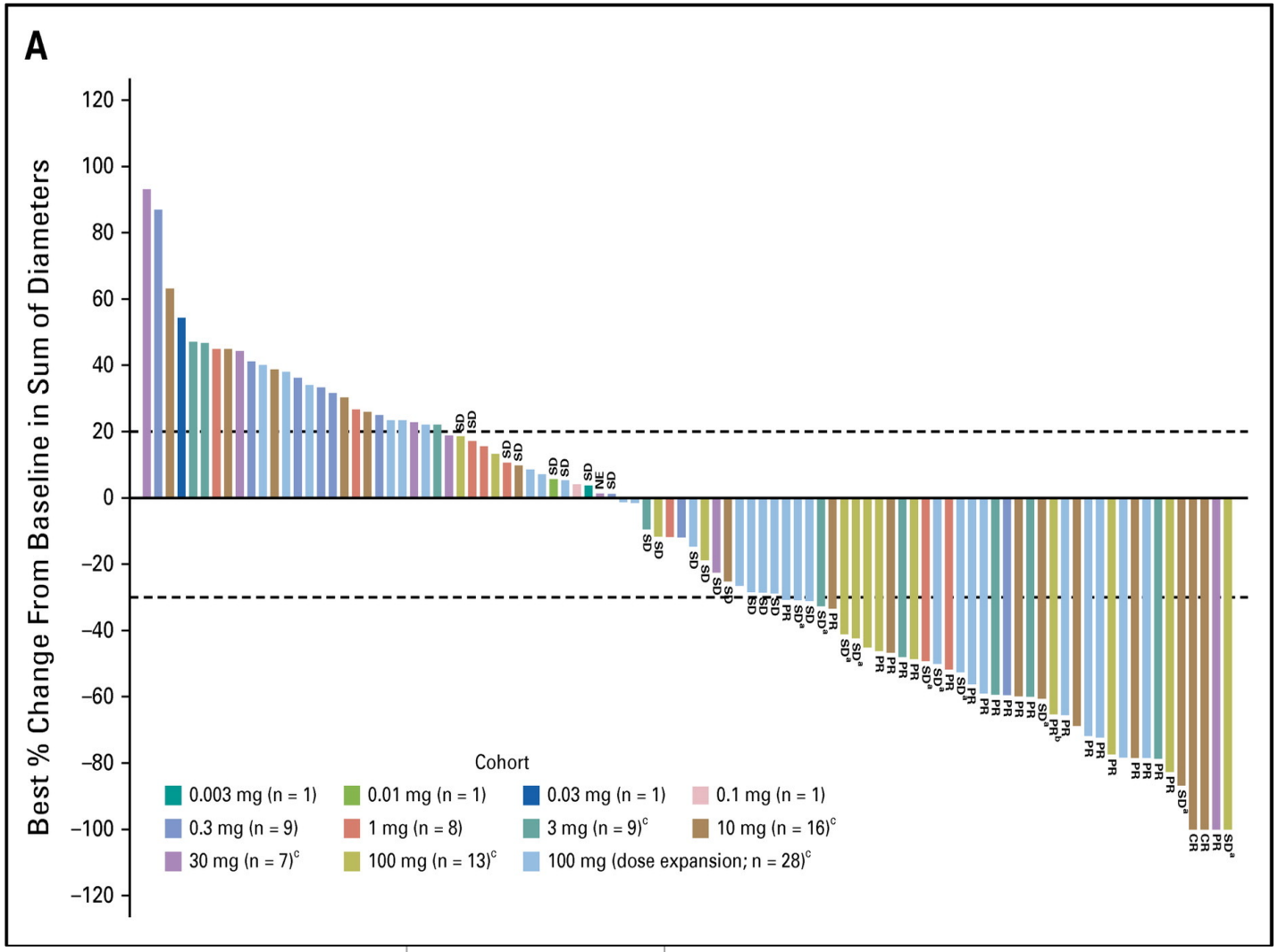
**e** Rechallenging with the original regimen or similar platinum-based regimen, as shown on SCL-E 1, is recommended if there has been a disease-free interval of more than 6 months and may be considered if there has been a disease-free interval of at least 3 to 6 months.

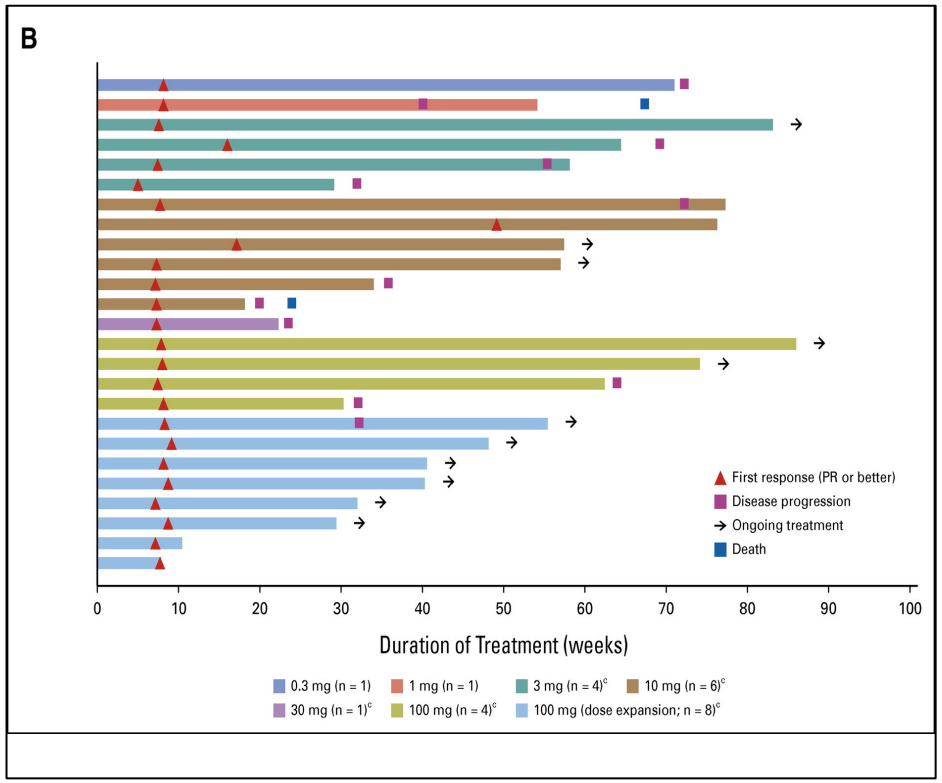
# Targeting DLL3 expression to improve the immune response in SCLC

- AMG 757 is a bispecific T cell engager (BiTE) combining the binding specificities for DLL3 and CD3 genetically fused to the IgG Fc region
- Designed to induce T cell proliferation and tumor cell lysis
- Adoptive cellular therapy using modified T-cells to express a CAR targeting DLL3



# Tarlatamab Response in SCLC patients




*Paz-Ares et al, JCO 2023*

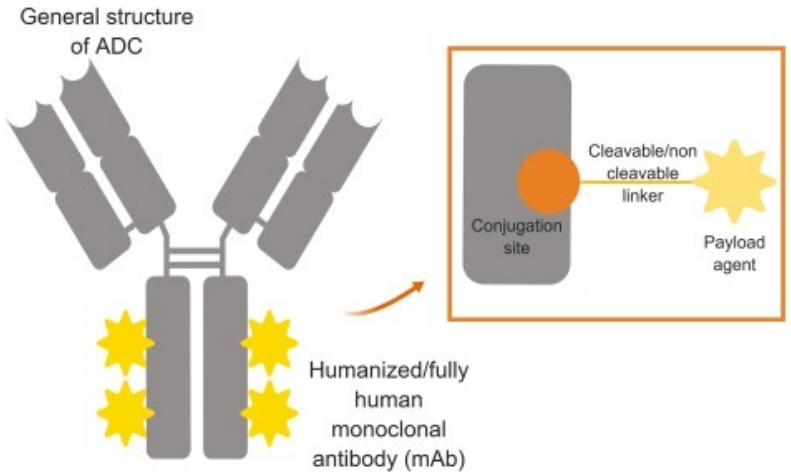
YaleNewHavenHealth
Smilow Cancer Hospital

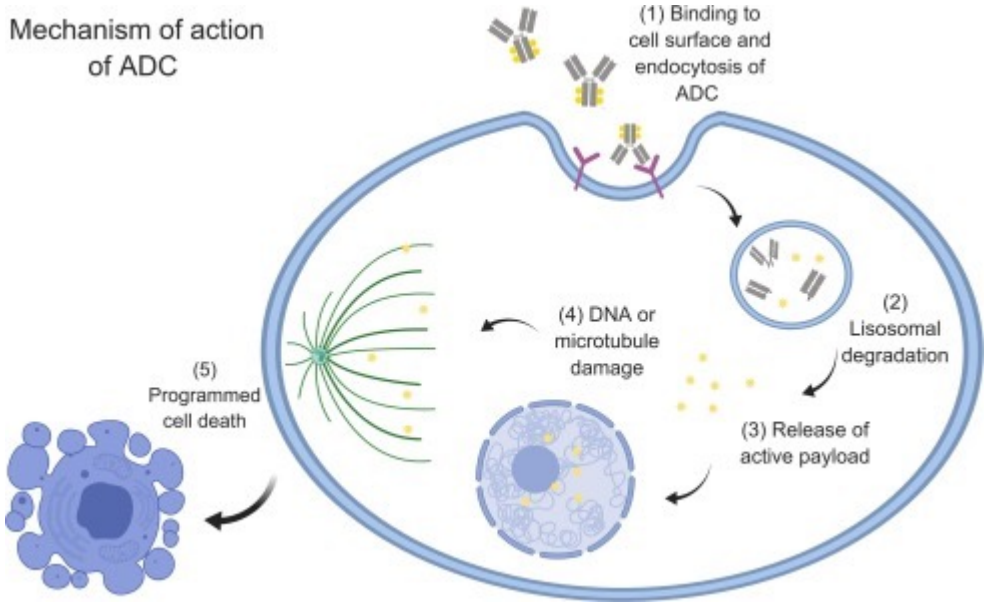
Yale CANCER CENTER
A Comprehensive Cancer Center Designated by the National Cancer Institute

Yale SCHOOL OF MEDICINE

# ADCs in SCLC

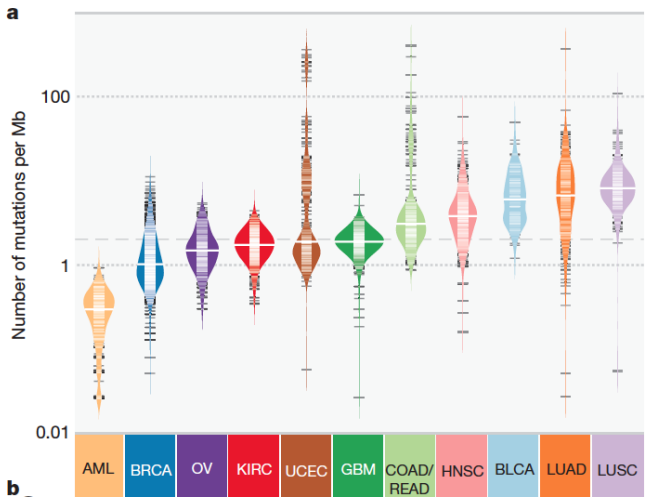
- DLL3
  - RovaT discontinued
- TROP2
  - IMMU-132
- B7-H3
  - DS-7300 (I-DXD)
- SEZ6
  - ABBV-011, -706
- CEACAM 5



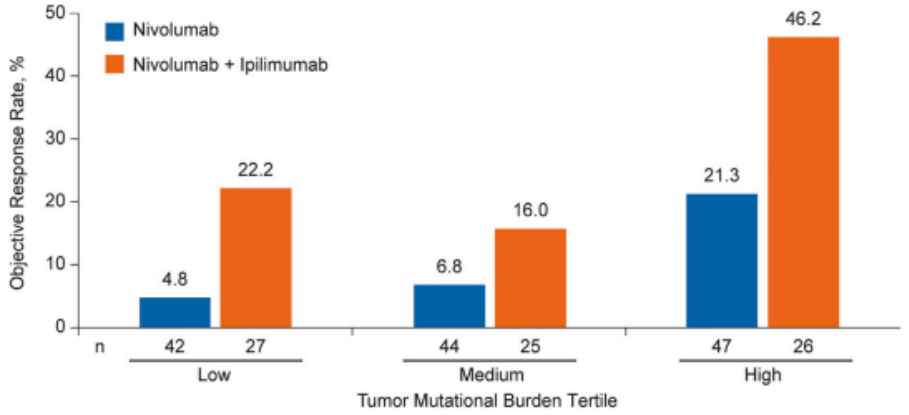

*Ricciuti, B, et al, Sem Cancer Biol 2021, 69:268-278*

# The Search for a Biomarker for Immune Checkpoint Inhibitors is Ongoing




Tumor Mutational Burden: A potential biomarker?

CHECKMATE 032: TMB as a Predictor for Response to Immunotherapy in SCLC

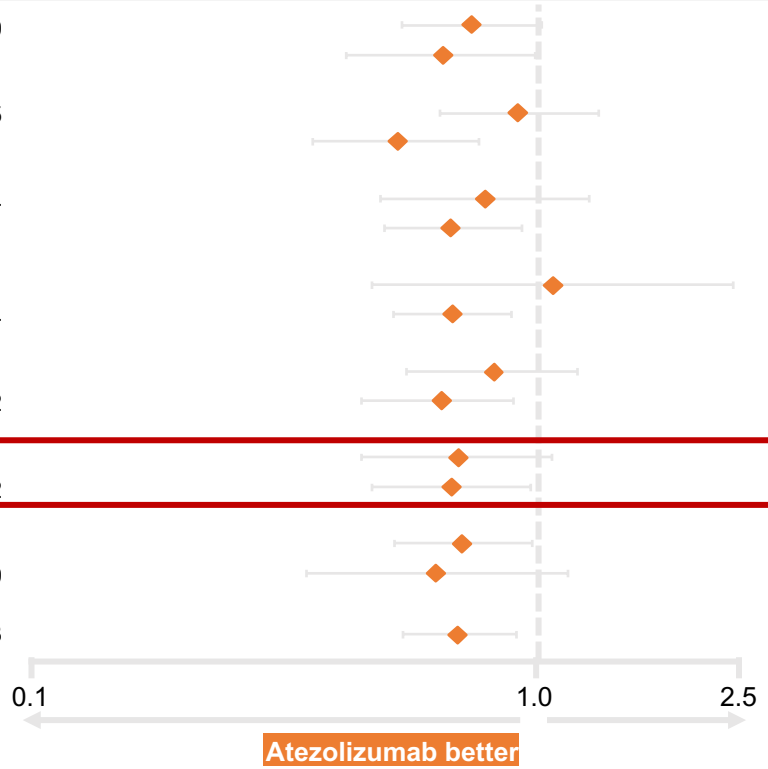



For nivo/ipi pts, high TMB cohort- RR 46.2 % and 1YOS 62.4 %!

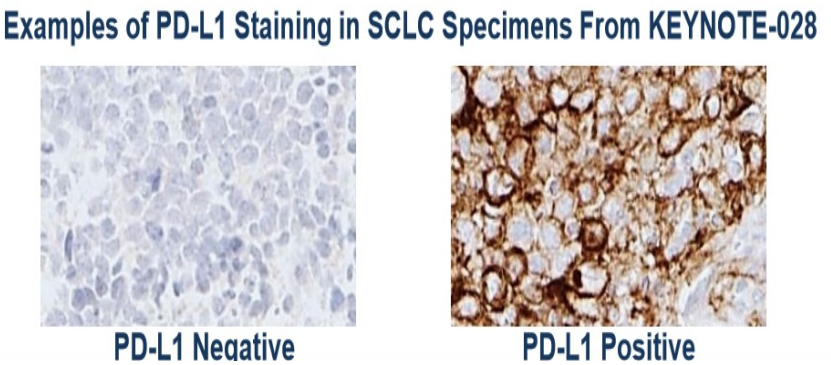
*Hellmann, Cancer Cell 2018*

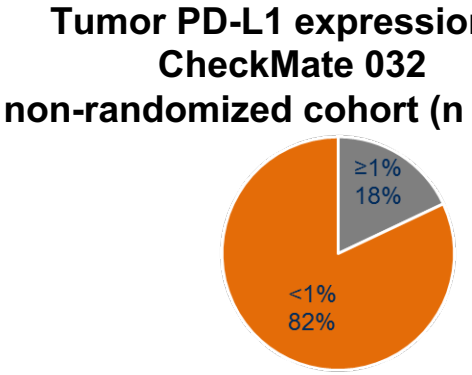
# TMB is not predictive of benefit from atezo + chemotherapy

| 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) |



# PD-L1 expression in SCLC: not a clearcut biomarker




- PD-L1 combined score = ratio of PD-L1 positive cells (including tumor cells, lymphocytes and macrophages) to the total number of tumor cells
- Phase 2 KN-028 trial of pembro in SCLC showed that 39% of patients were PD-L1 positive (≥ 1)
- PD-L1 positivity predicted for higher response 35.7% vs 6% and longer PFS and OS on pembro

| ORR by Tumor PD-L1 Expression | | |
|---|---|---|
| | ORR, % (n/N) | |
| PD-L1 expression | Nivolumab (n = 98) | Nivolumab + Ipilimumab (n = 61) |
| Less than 1% | 14 (9/64) | 32 (10/31) |
| 1% or more | 9 (1/11) | 10 (1/10) |

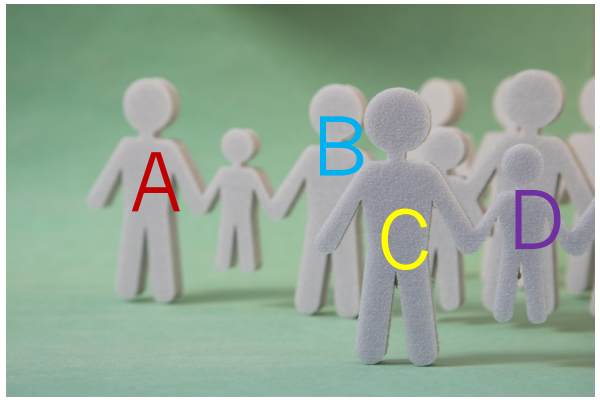
*Hellman MD et al. Presented at ASCO Meeting 2017*

*Ott, et al, WCLC 2015, Chung HC, et al. ASCO 2018*

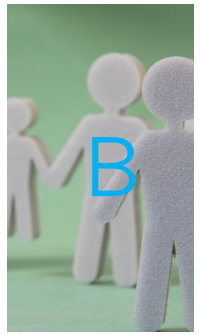
# The Promise of Personalized Medicine and Targeted Therapy

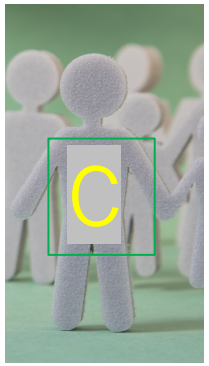

Treatment A

Patient Group




Treatment B



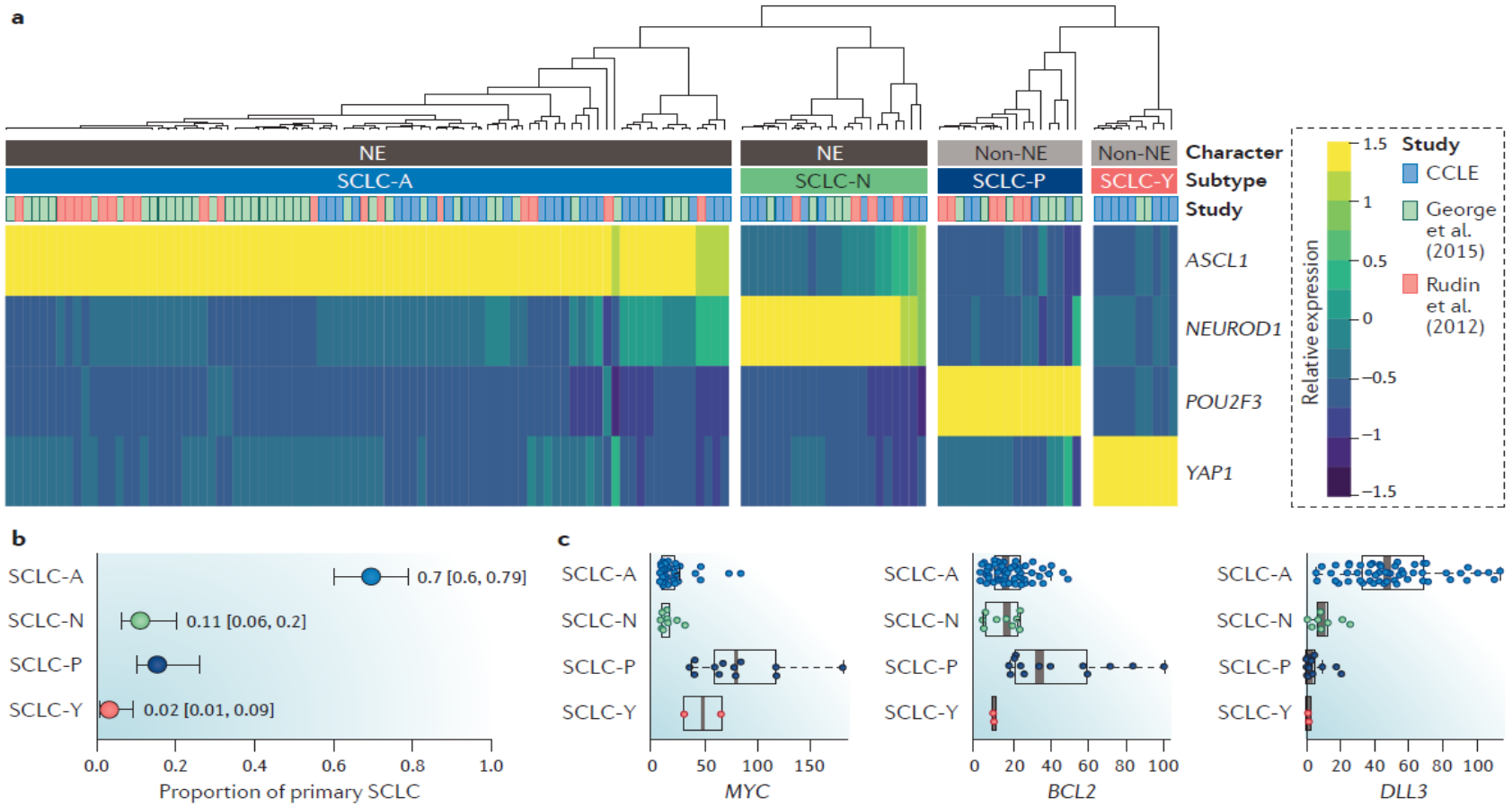

Treatment C

**Same Diagnosis**
Personalized treatment
to improve outcomes and
to reduce toxicities

Treatment D


- Image courtesy of Djem and Shutterstock.com.

# SCLC Biology: Molecular Subtypes by Expression of Key Transcriptional Regulators



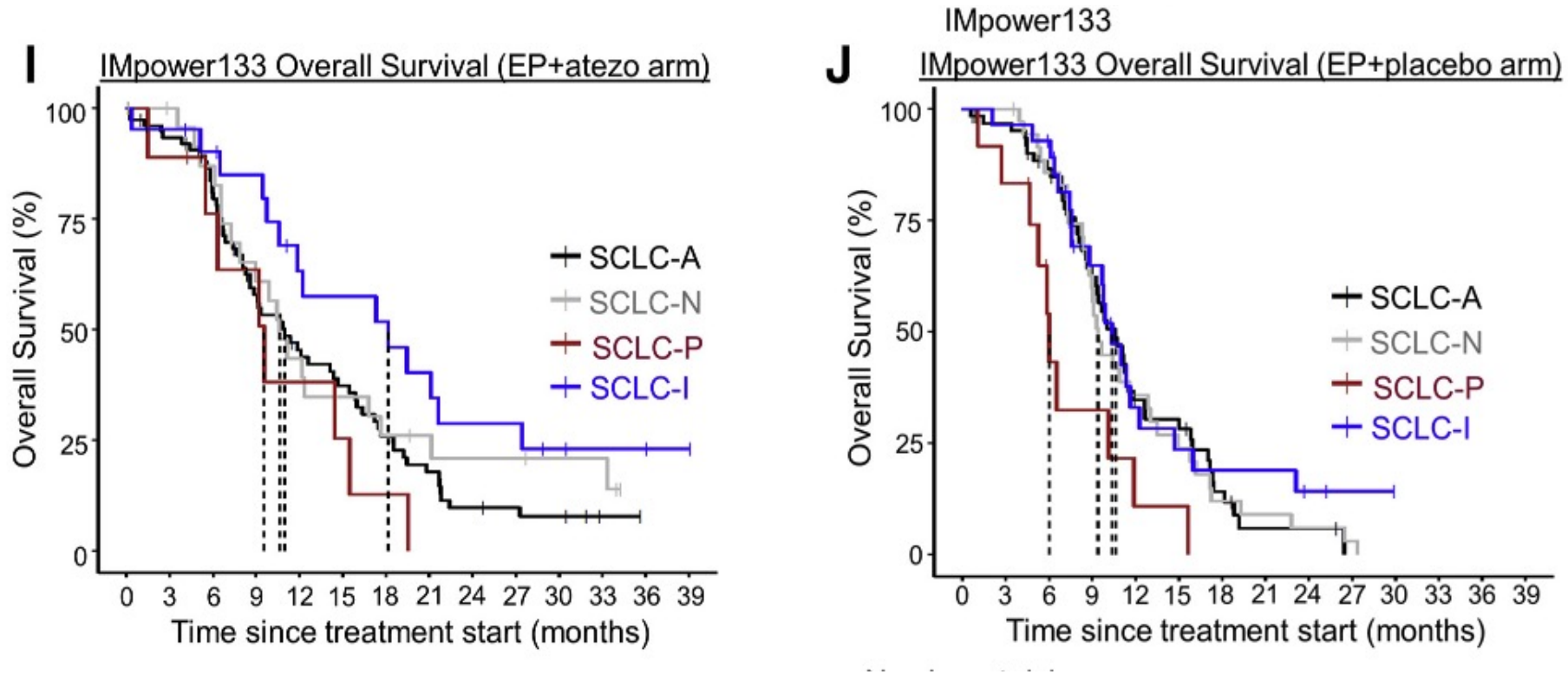

YaleNewHavenHealth
Smilow Cancer Hospital

Yale CANCER CENTER
A Comprehensive Cancer Center Designated by the National Cancer Institute

Yale SCHOOL OF MEDICINE

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

# Better OS for SCLC-I “Inflamed Subtype” in Impower133




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

# SCLC: Key Points

- Two new FDA approvals for Immunotherapy plus chemo in front-line therapy
- New second line FDA approval for lurbinectedin
- 2 single agent immunotherapy withdrawals in 3rd line-- need for further understanding of biomarkers in SCLC to understand which patients benefit from immunotherapy
- Need to develop options for patients who are refractory or resistant to immunotherapy
- Understanding the complexity and biology of SCLC may lead to more effective treatments

# Questions?