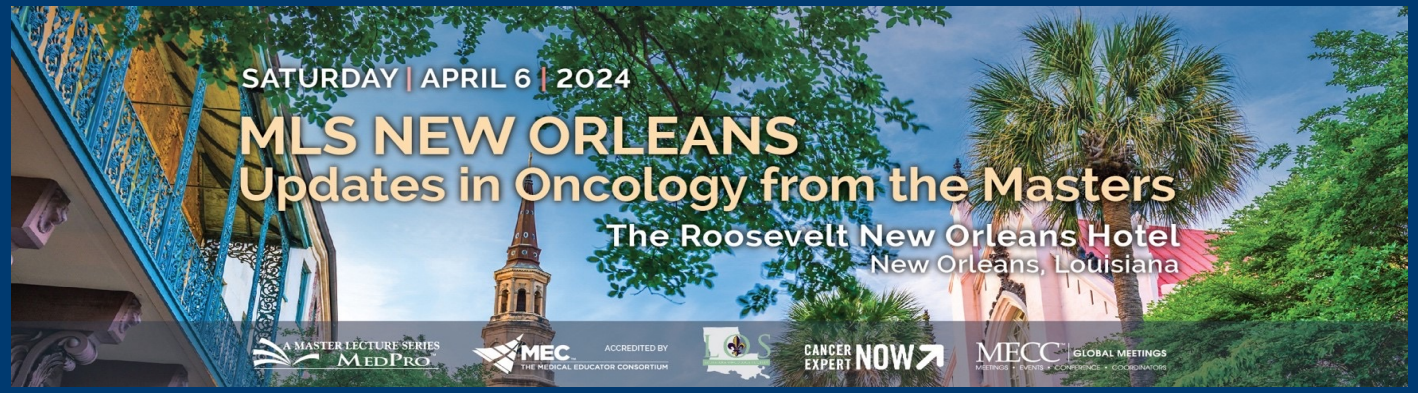

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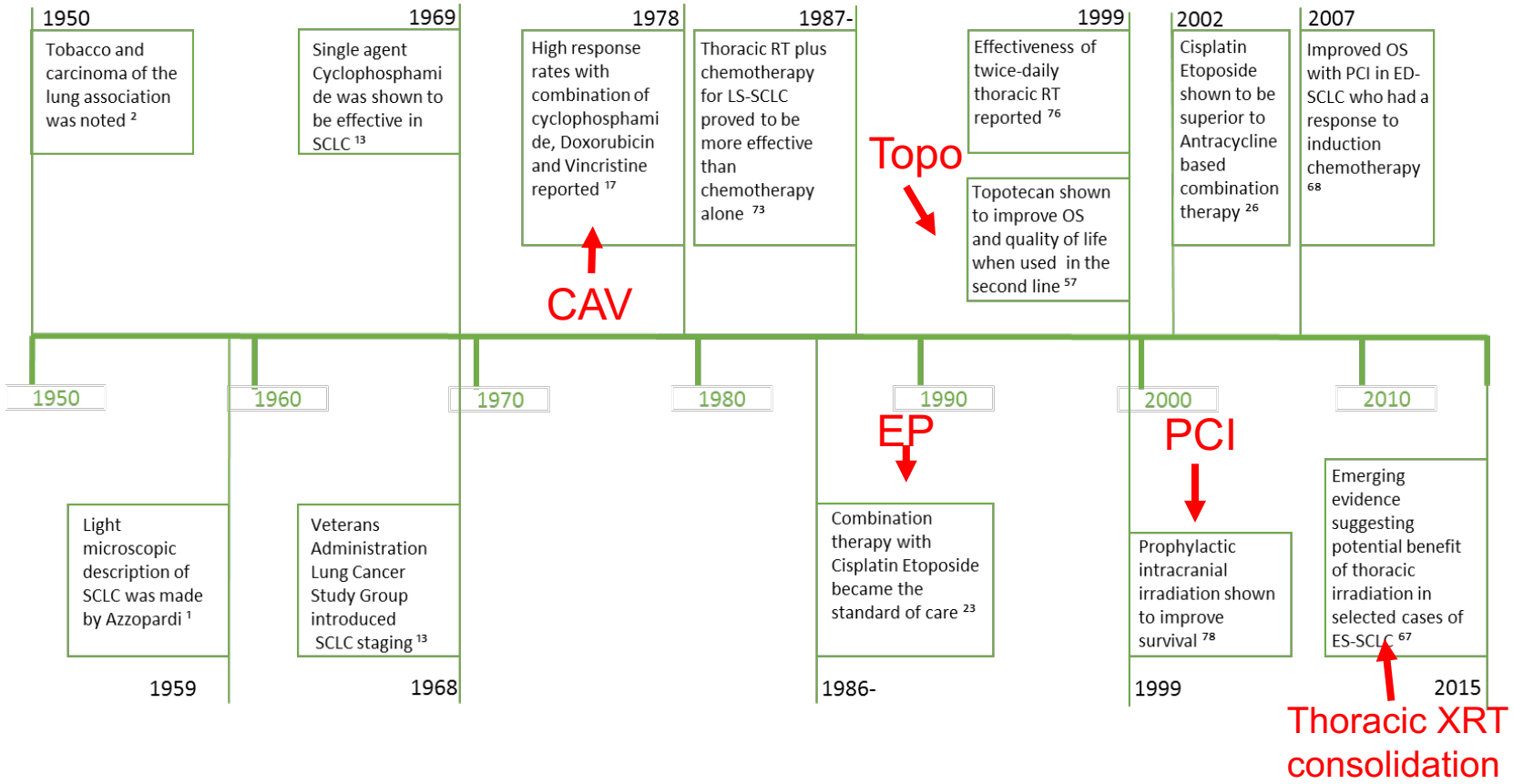
Yale CANCER CENTER

Small Cell Lung Cancer: 1L and Beyond

Michael J Grant MD
Assistant Professor, Division of Thoracic Medical Oncology
Yale University School of Medicine
Yale Cancer Center

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



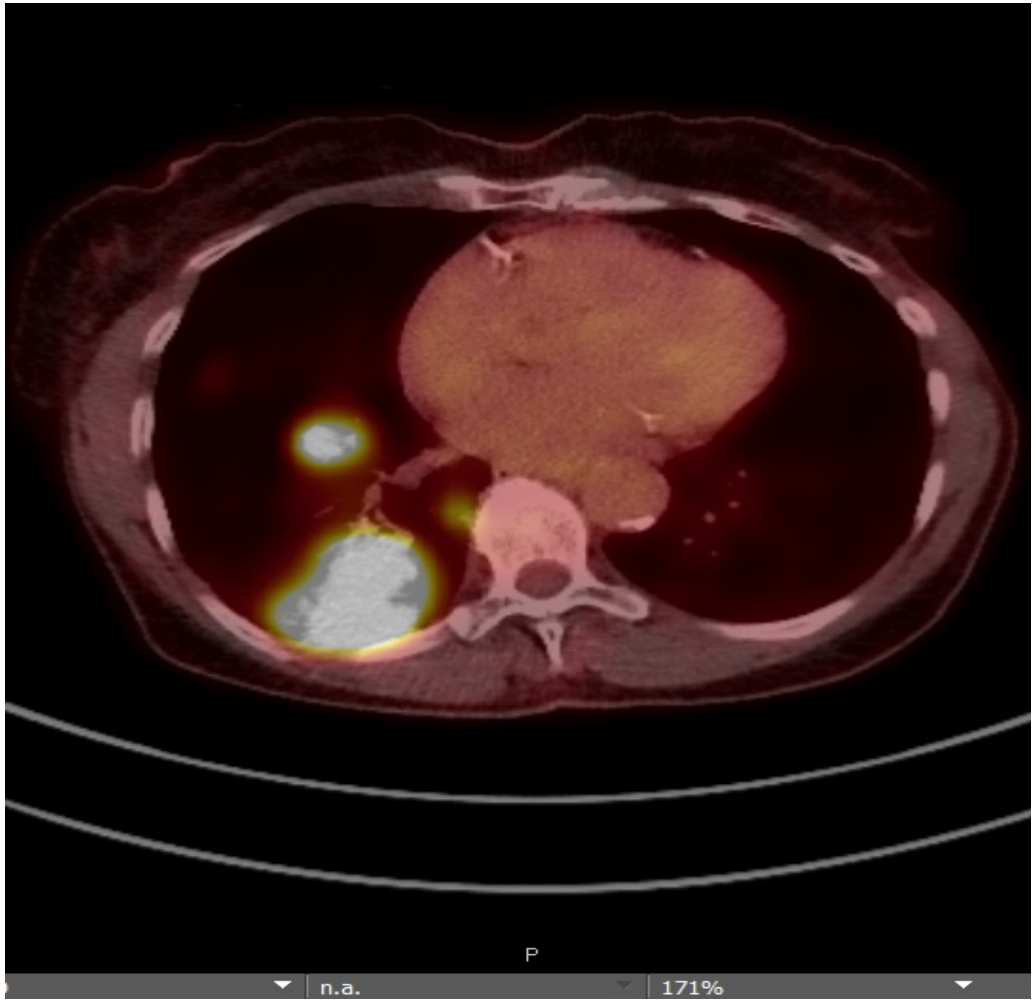
Landscape is changing NOW–
with immunotherapy and advances in understanding SCLC biology

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

Case # 1 Presentation at Diagnosis

- 65-year-old female (40 py tobacco history) presented with weight loss over several months, worsening SOB on exertion, abdominal discomfort
- Physical exam reveals neck and right axillary adenopathy
- PET scan shows 7.2 cm RLL mass, additional hypermet nodules in RLL, extensive regional nodal involvement in right hilar, mediastinal nodes, axillary nodes.
- Brain MRI negative
- Biopsy of LN reveals small cell carcinoma, positive for synaptophysin, chromogranin, TTF1, Ki-67 is 90%

How would you treat this patient?



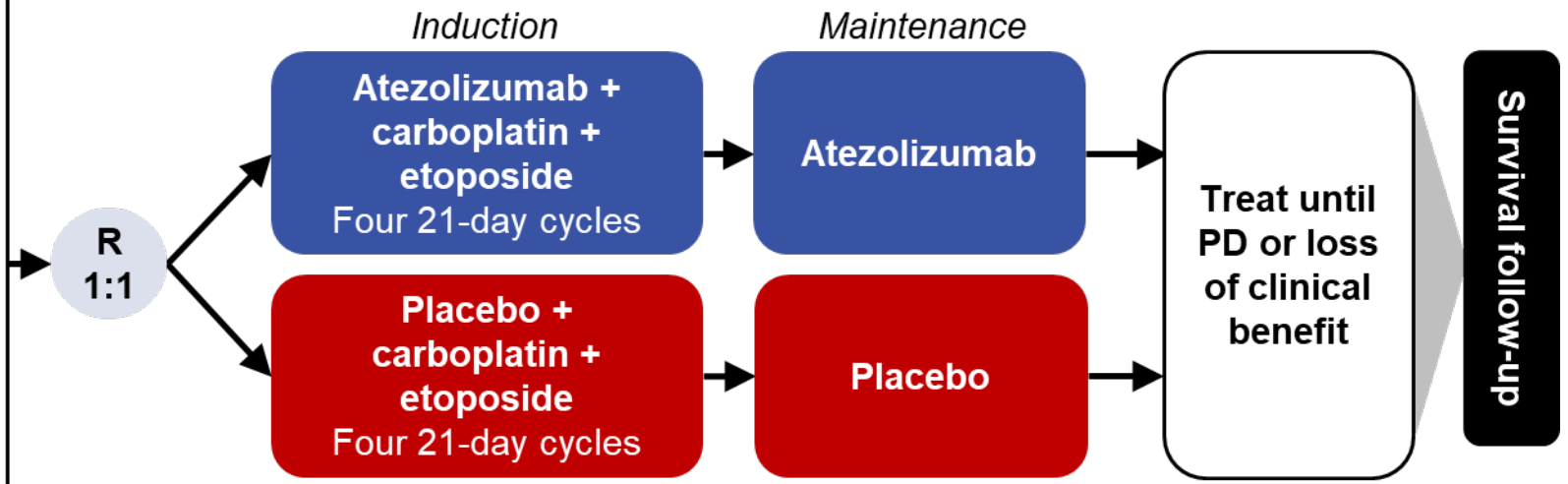
IMpower133: Atezolizumab/Carboplatin/Etoposide

- 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

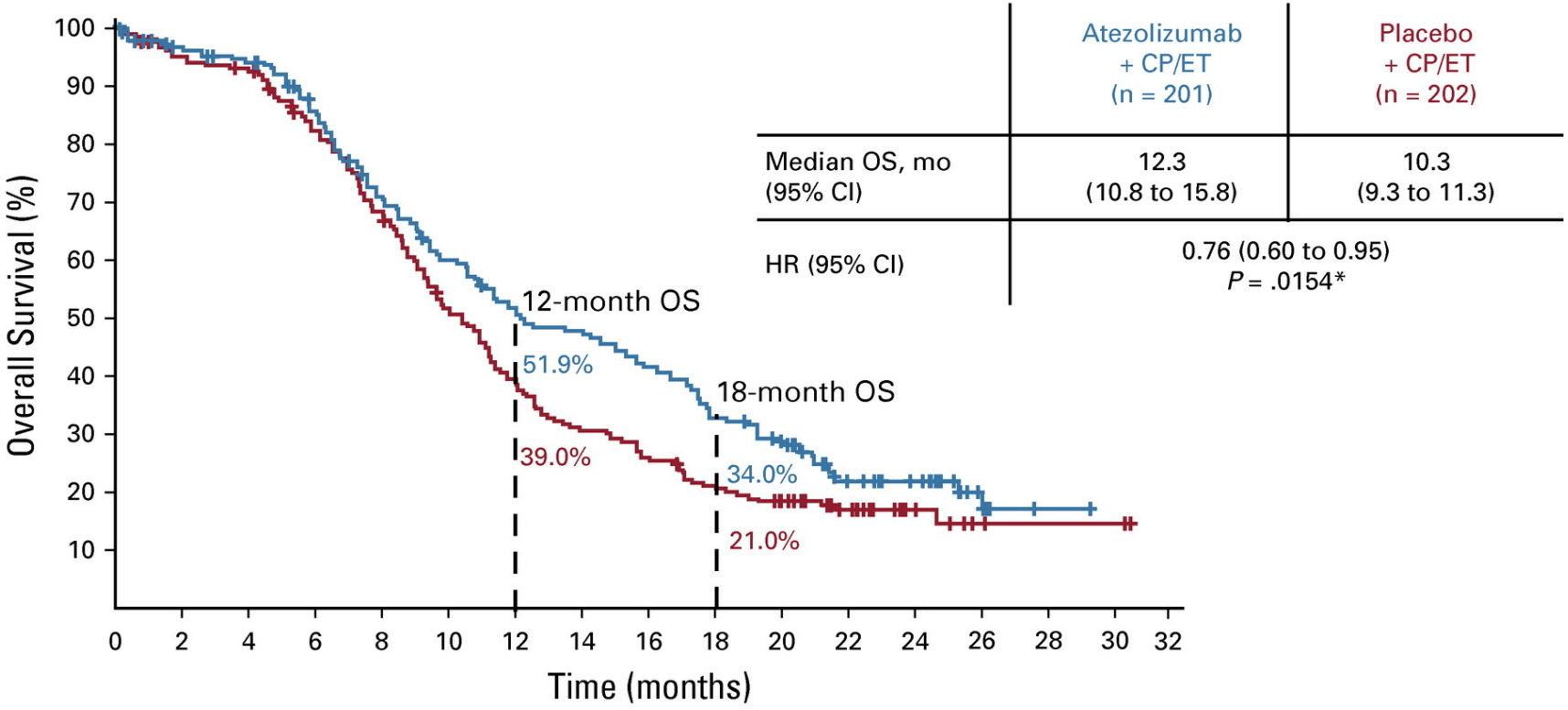


Primary endpoints

- ✓ OS
- ✓ Investigator-assessed PFS

IMpower133: Atezolizumab/Carboplatin/Etoposide

A



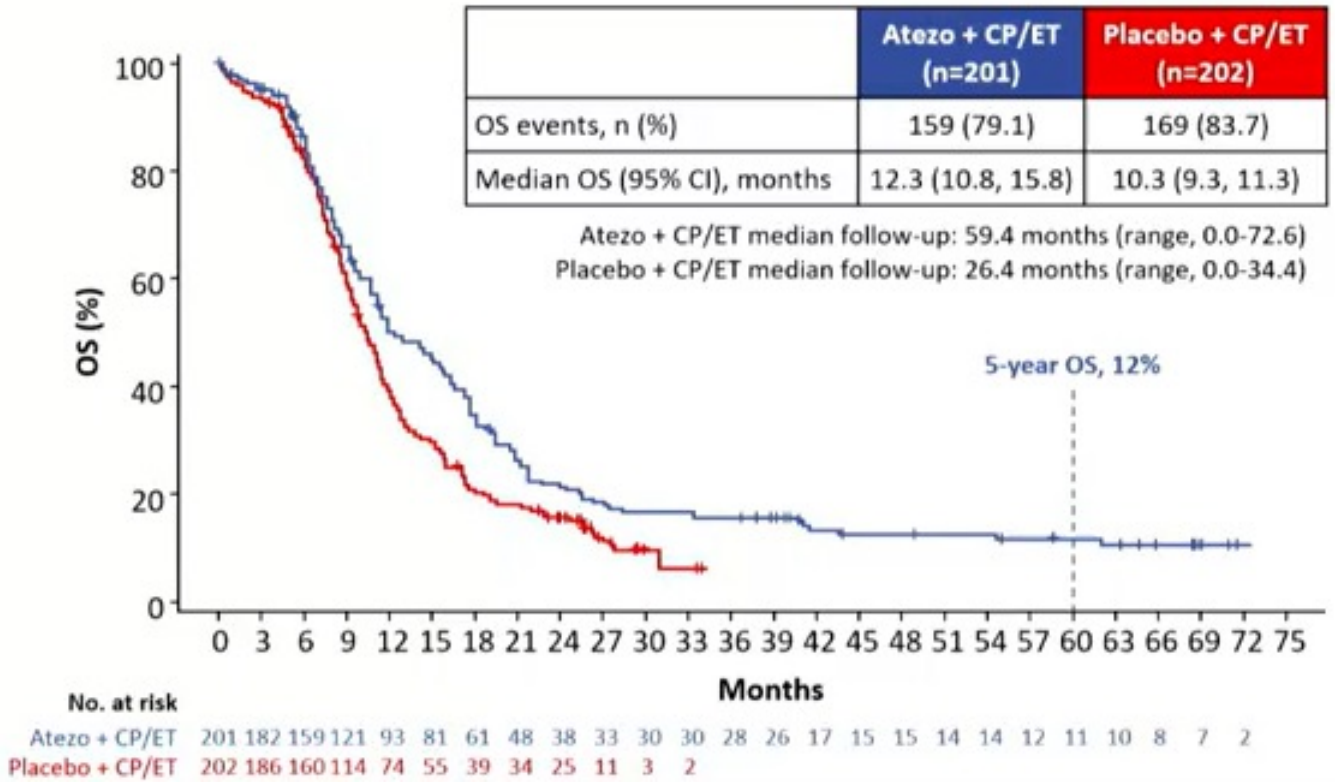
	Atezolizumab + CP/ET (n = 201)	Placebo + CP/ET (n = 202)
Median OS, mo (95% CI)	12.3 (10.8 to 15.8)	10.3 (9.3 to 11.3)
HR (95% CI)	0.76 (0.60 to 0.95) *P* = .0154*	

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

Liu et al JCO 2023. Median Follow up 22.9 months

Merged Impower133/ Imbrella A analysis



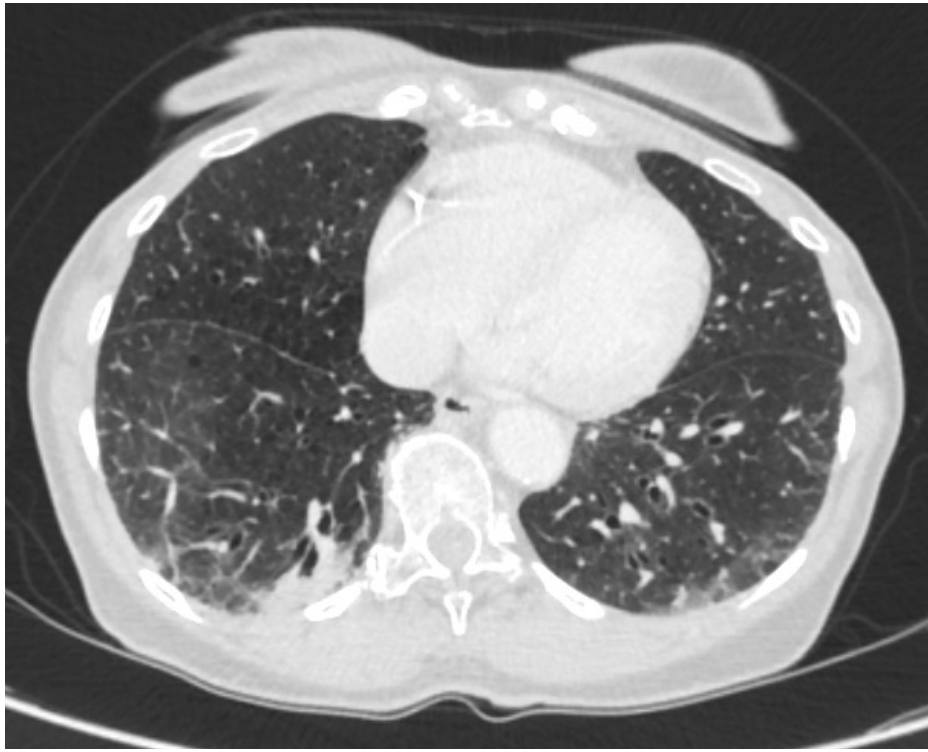
OS rate (95% CI), %	IMpower133 and IMbrella A Atezo + CP/ET (n=201)	IMpower133 only Placebo + CP/ET (n=202)
1-year	52% (45-59)	39% (32-46)
2-year	22% (16-28)	16% (11-21)
3-year	16% (11-21)	NE[a]
4-year	13% (8-18)	NE[a]
5-year	12% (7-17)	NE[a]

Liu et al. WCLC 2023

Case # 1-cont

- The patient has an 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
- Any Grade: 95% vs 92%
- G3/4: 57 vs 56%
- G5: 1.5 vs 1.5%

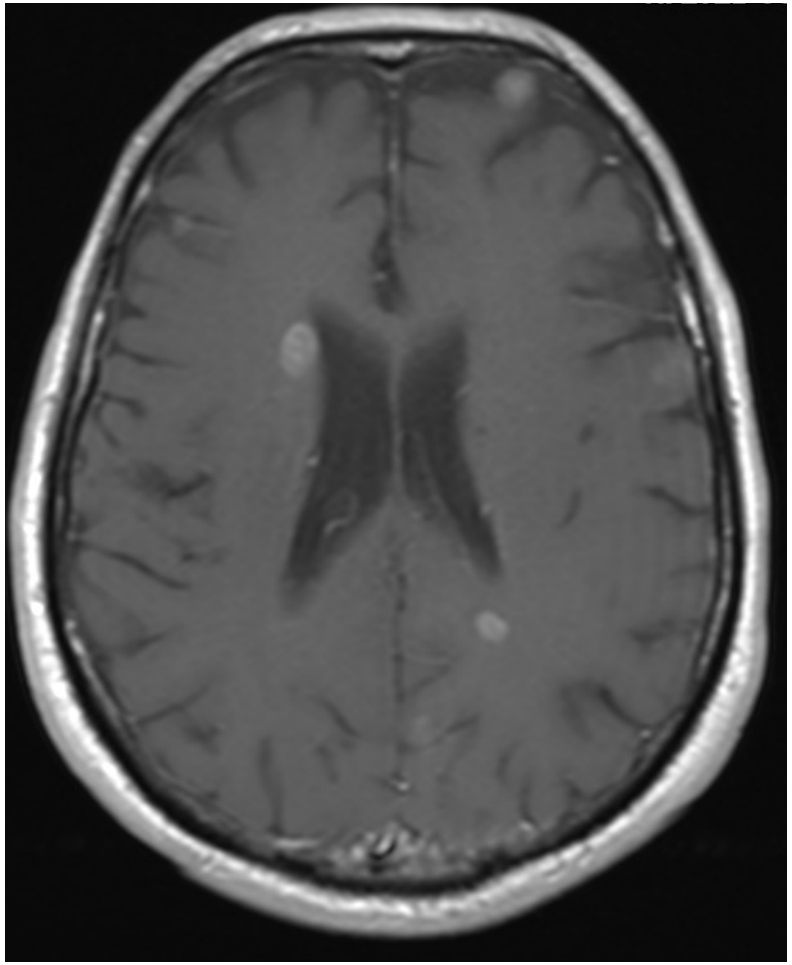
Maintenance Atezo treatment duration, median:
- 4.7 vs 4.1 mo

Liu et al JCO 2023.

Case # 2

- 67-year-old male (50 py tobacco history) presented with weight loss over several months, worsening SOB on exertion
- 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?



NCCN Guidelines Version 2.2024
Small Cell Lung Cancer

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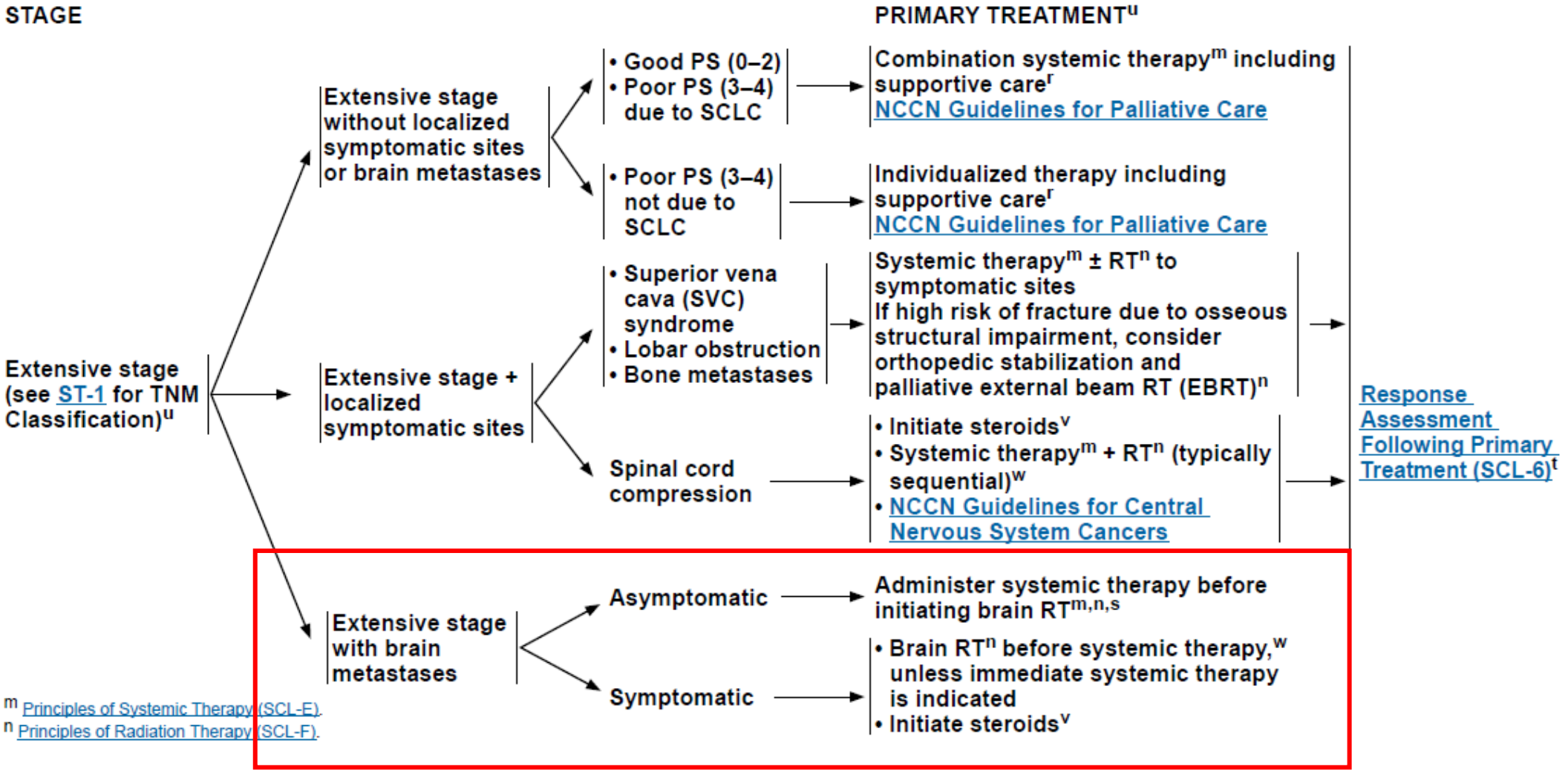


[m] Principles of Systemic Therapy (SCL-E).
[n] Principles of Radiation Therapy (SCL-F).

CASPIAN Study Design

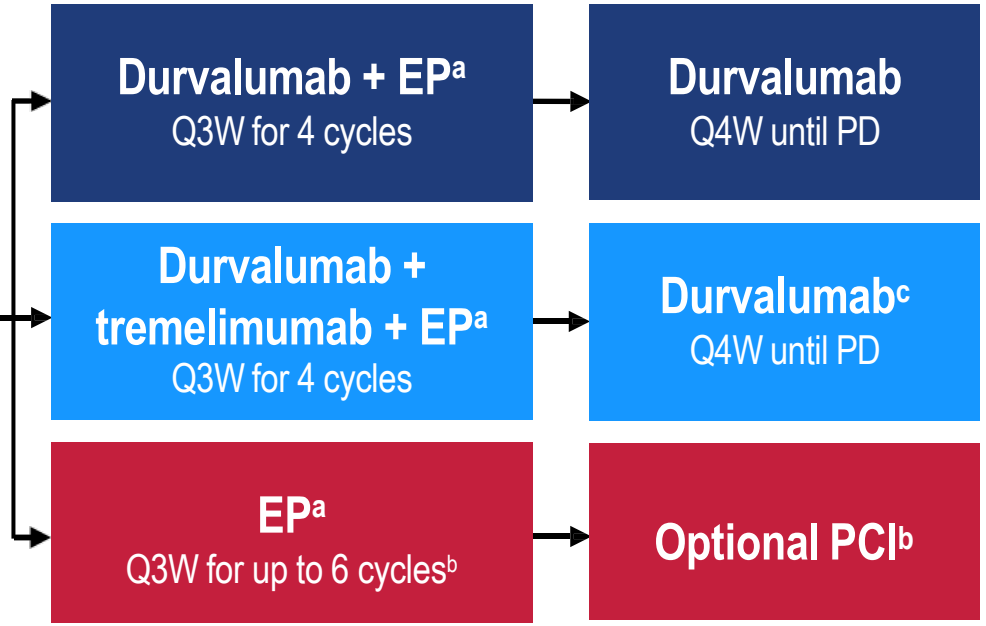
Phase 3, global, randomized, open-label, active-controlled, multicenter study

- 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

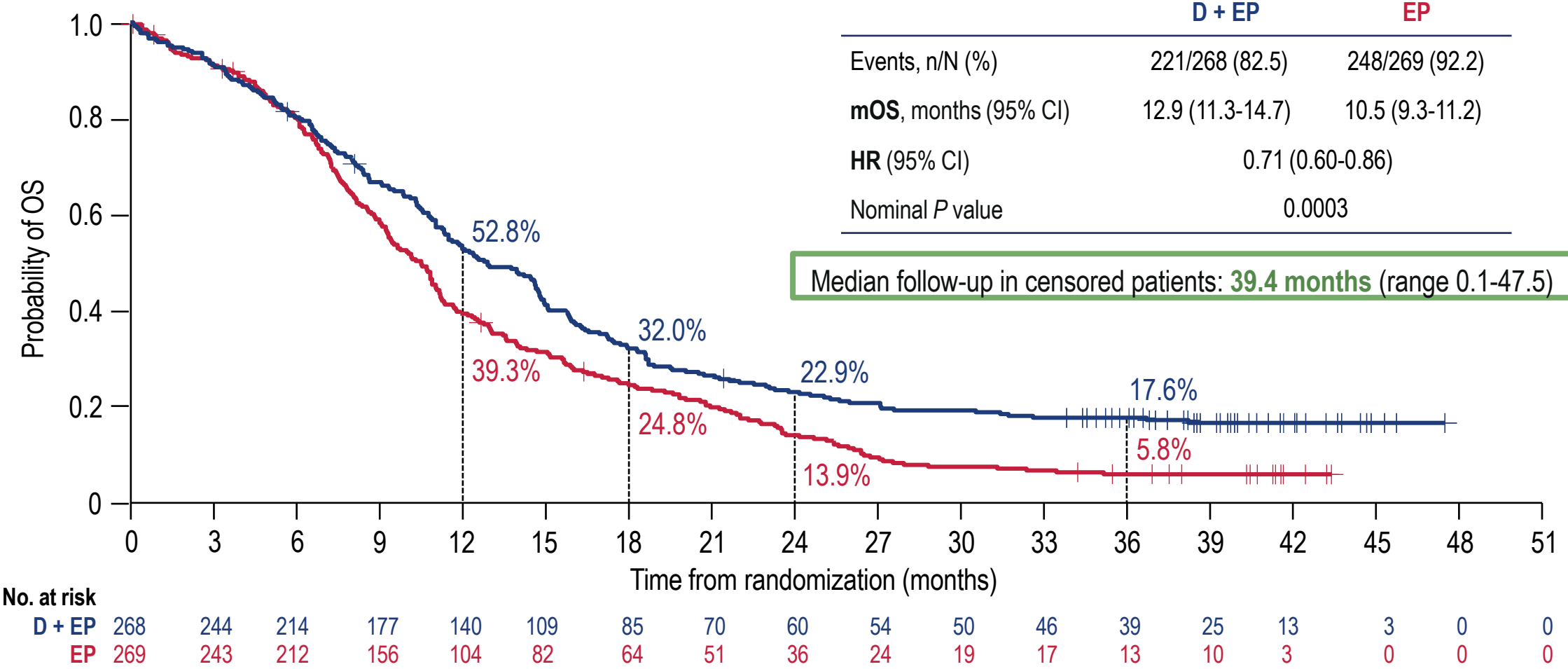
[a]EP consists of etoposide 80-100 mg/m^2 with either carboplatin AUC 5-6 or cisplatin 75-80 mg/m^2, durvalumab dosed at 1500 mg, tremelimumab dosed at 75 mg. [b]Patients could receive an additional 2 cycles of EP (up to 6 cycles total) and PCI at the investigator's discretion. [c]Patients received an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

Paz-Ares LG, et al. *Ann Oncol*. 2021

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)

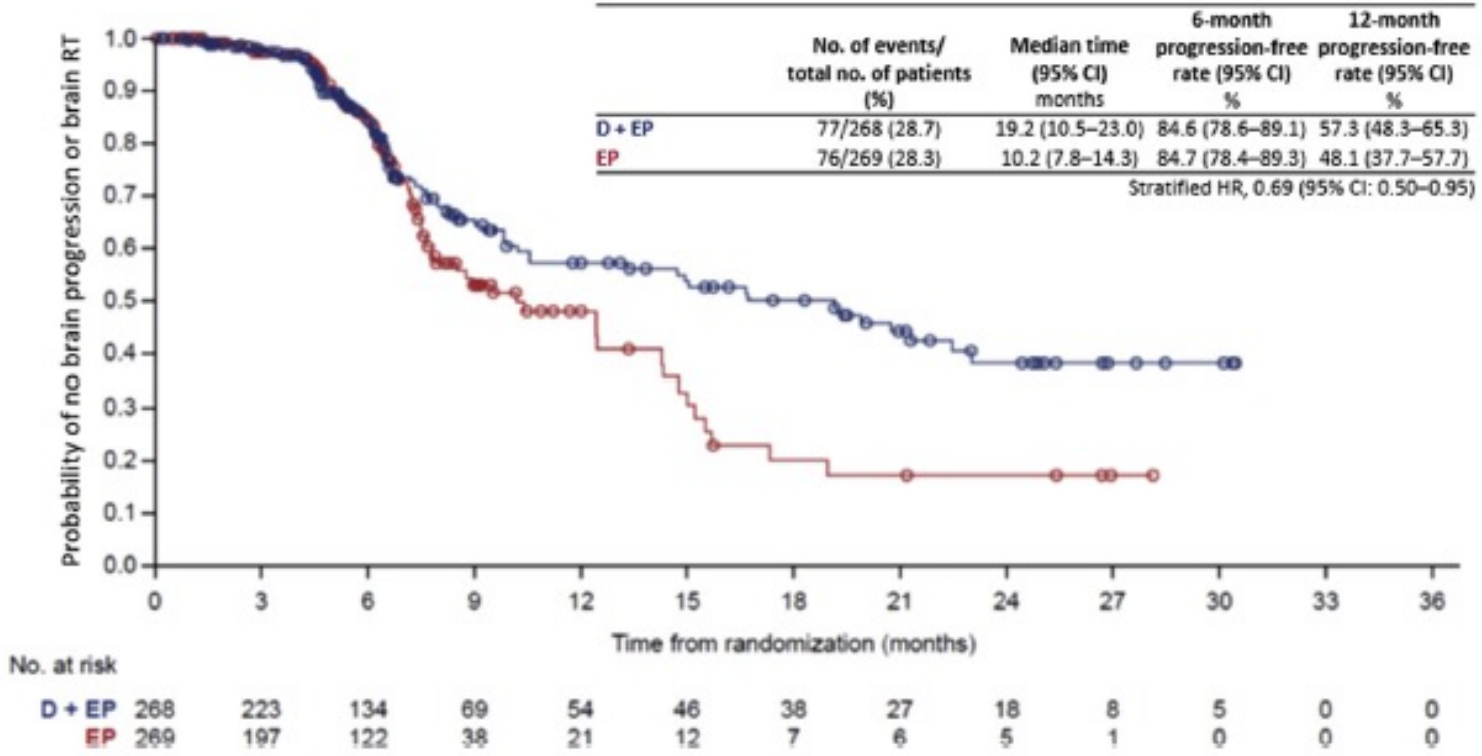


No. at risk

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.

CASPIAN- Patients with brain metastases:



	No. of events/ total no. of patients (%)	Median time (95% CI) months	6-month progression-free rate (95% CI) %	12-month progression-free rate (95% CI) %
D + EP	77/268 (28.7)	19.2 (10.5–23.0)	84.6 (78.6–89.1)	57.3 (48.3–65.3)
EP	76/269 (28.3)	10.2 (7.8–14.3)	84.7 (78.4–89.3)	48.1 (37.7–57.7)

Stratified HR, 0.69 (95% CI: 0.50–0.95)

- 10% brain mets on each arm
- Majority untreated with RT
- In patients w/o BM at baseline, similar rate of subsequent brain RT (~21%) in both arms

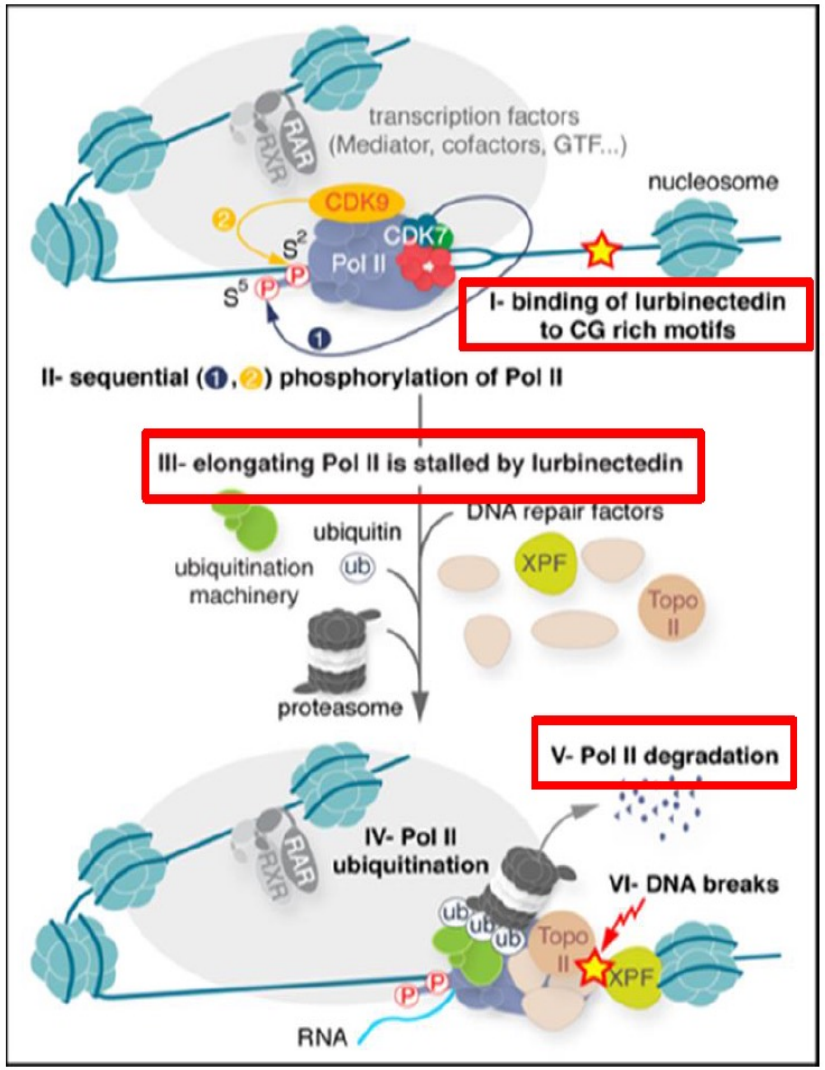
Chen et al. JTOCCR 2022

FDA approvals for 1L ES-SCLC: Updated Analyses

	IMpower133/Imbrella A updated (2023)	CASPIAN updated (2021)
Median follow up	59.4 mo (atezo arm)	39.4 mo
mOS	12.3 vs 10.3 mo	12.9 vs 10.5 mo
HR	0.76, p=0.0154	0.71, p=0.0003
3YOS	16% vs NE	17.6 vs 5.8%
Eligibility	Treated brain mets only	Asymptomatic brain mets allowed
Platinum	Carboplatin	Cis or carboplatin

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%

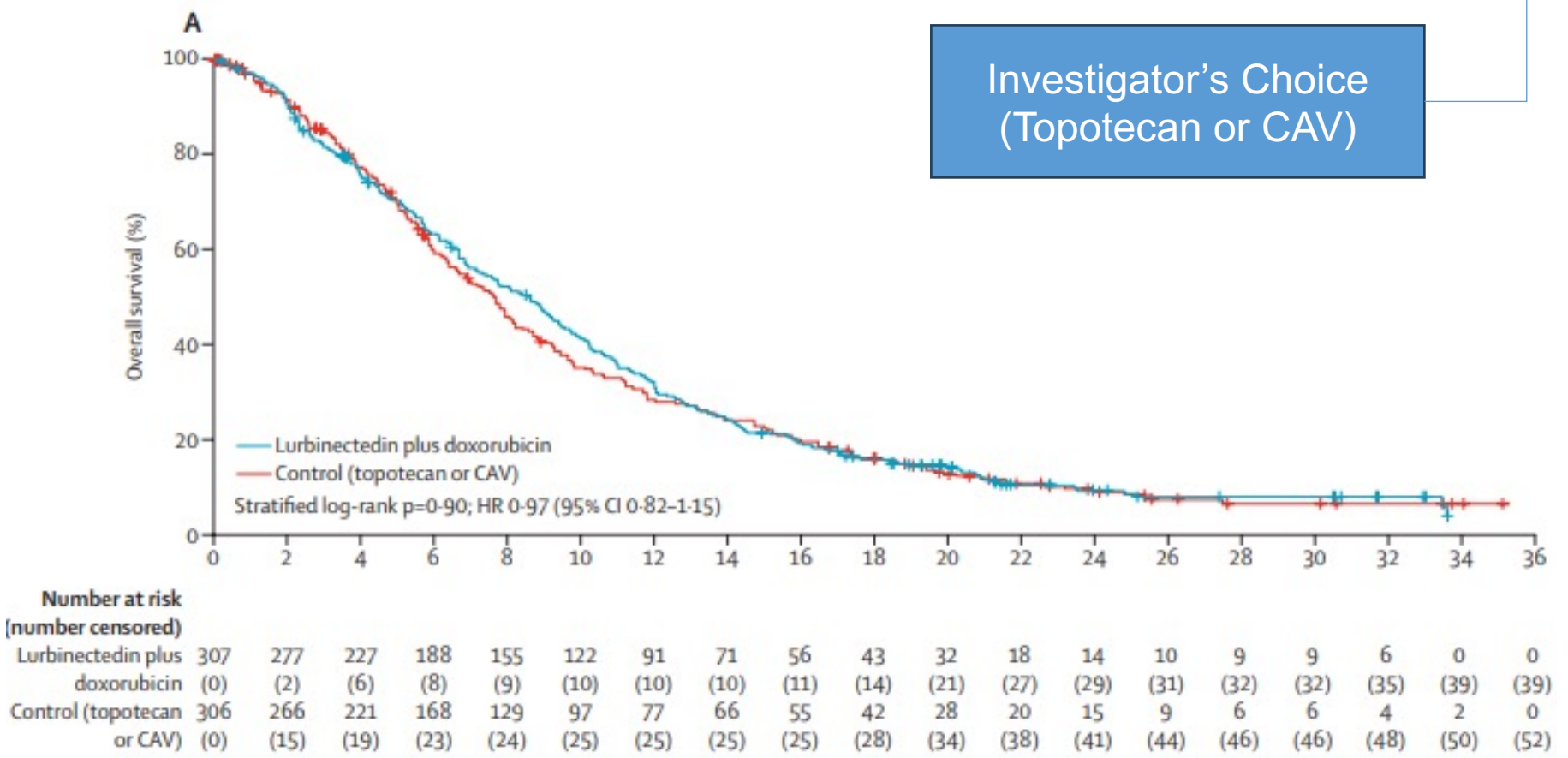
Trigo et al, Lancet Oncol 2021; Subbiah et al, Lung Cancer 2020

Phase III ATLANTIS Study: Relapsed SCLC

Lurbinectidin 2mg/m2 + Doxorubicin 40mg/m2

Investigator's Choice (Topotecan or CAV)

→ OS



Aix et al. Lancet Resp Med, 2023

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]

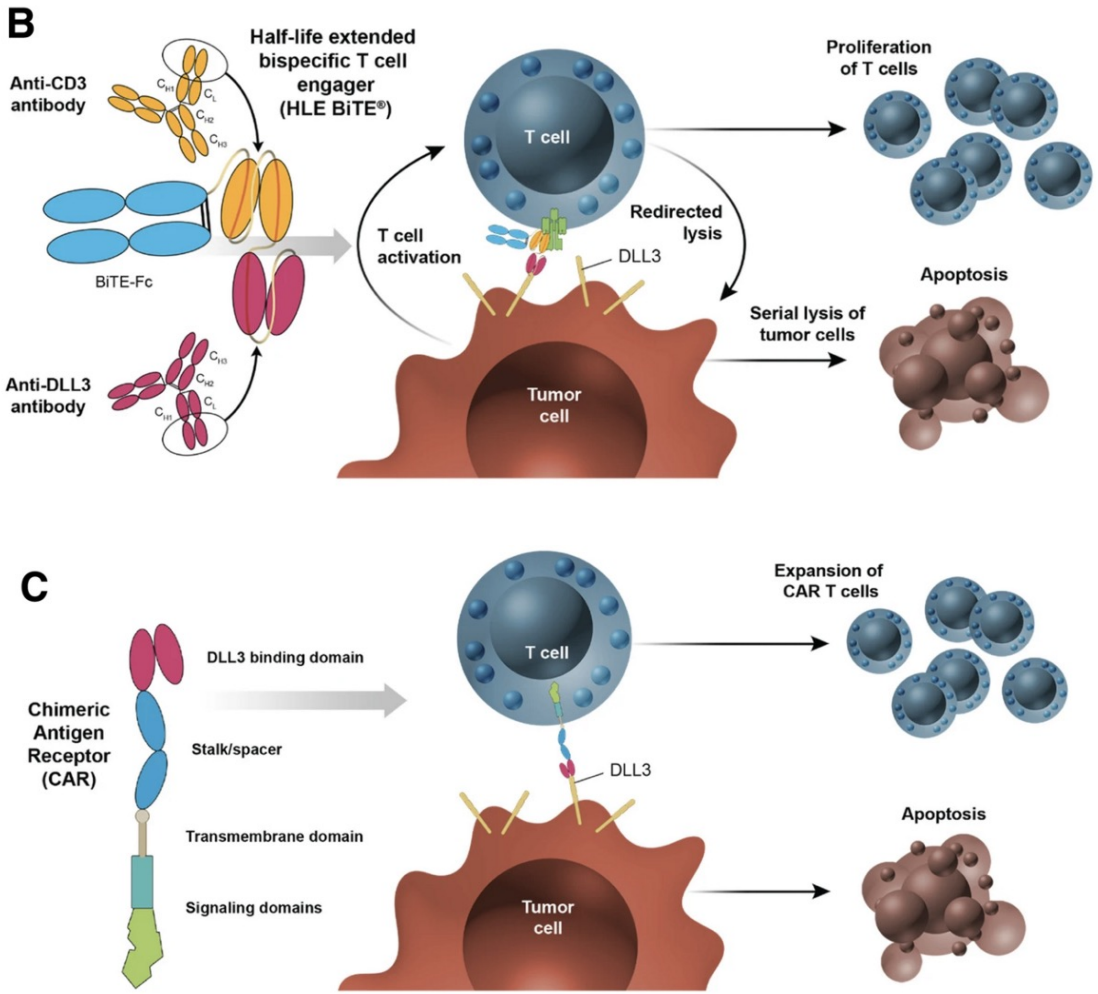
b Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or concurrent use of immunosuppressive agents.

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.

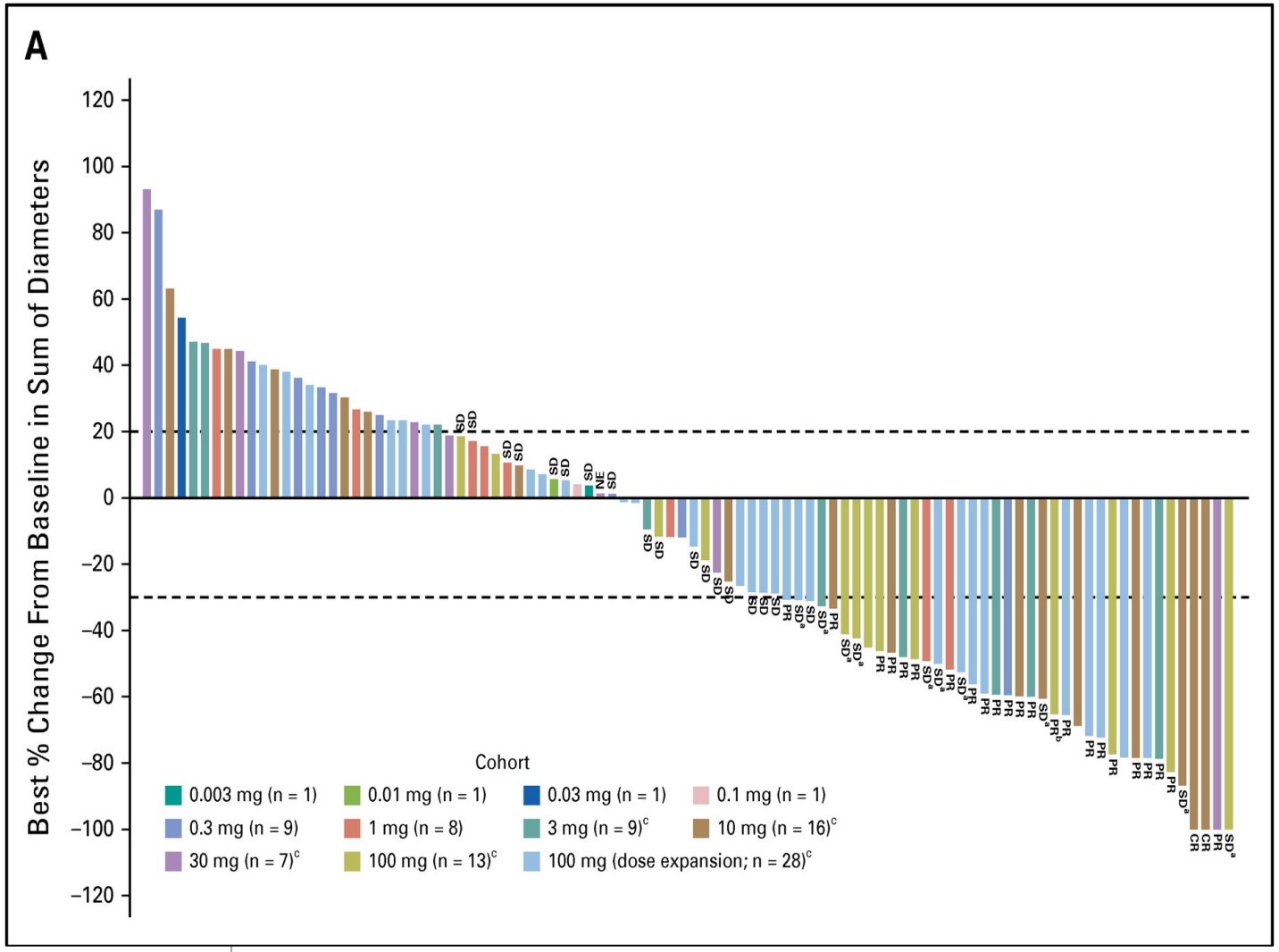
Targeting DLL3 expression to improve the immune response in SCLC

- 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



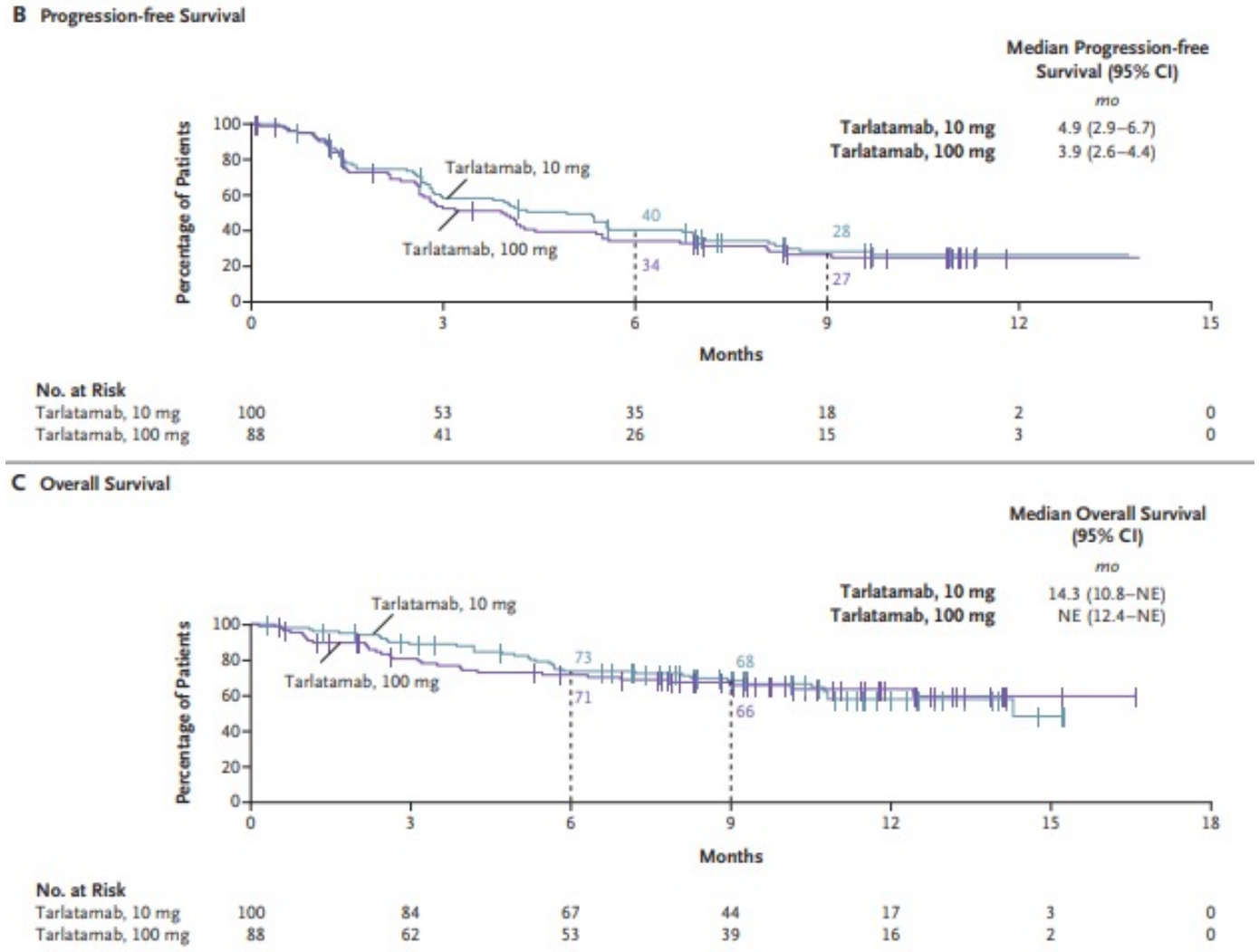
Owen DH, et al. J Hematol Oncol 2019

Tarlatamab activity in patients with SCLC



Paz-Ares et al, JCO 2023

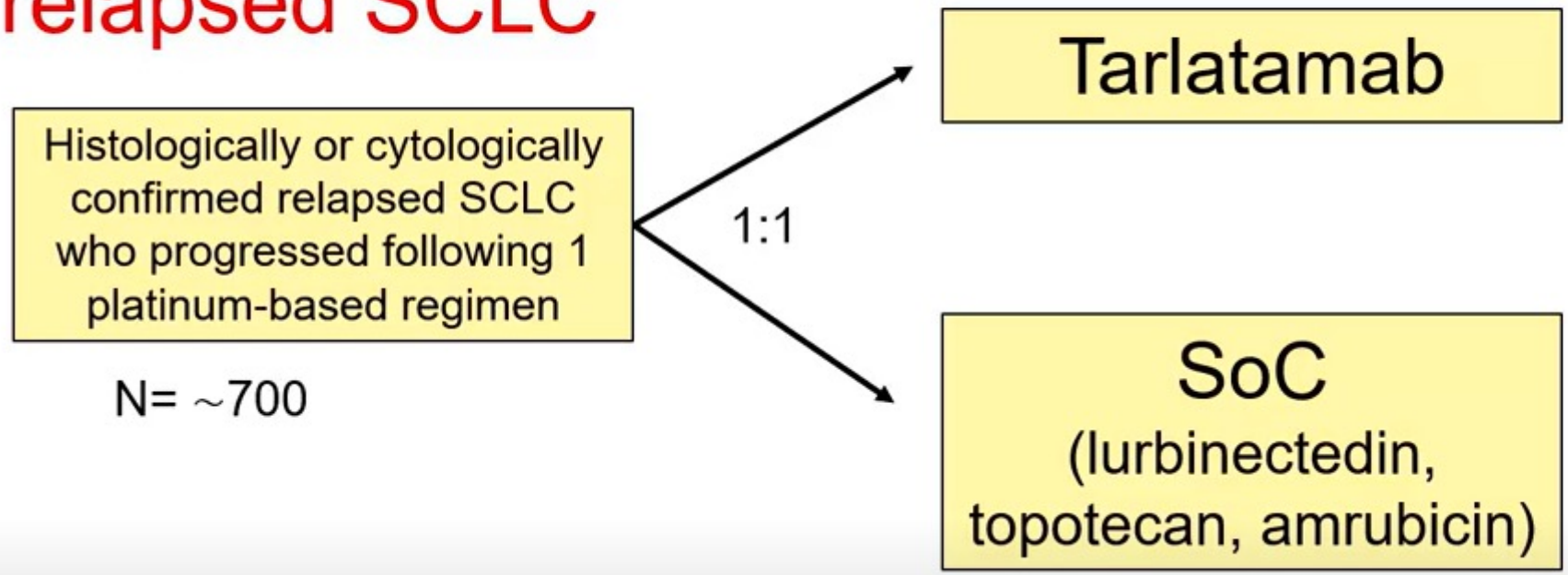
Tarlatamab



Toxicity	Tarlatamab 10mg
CRS	All: 56% Grade ≥3: 3% Discontinue/ death: 0%
ICANS	All: 12% Grade ≥3: 0% Discontinue/ death: 0%
TRAEs	All: 85% Grade ≥3: 15% Discontinue/ death: 3%

Ahn et al. NEJM 2023

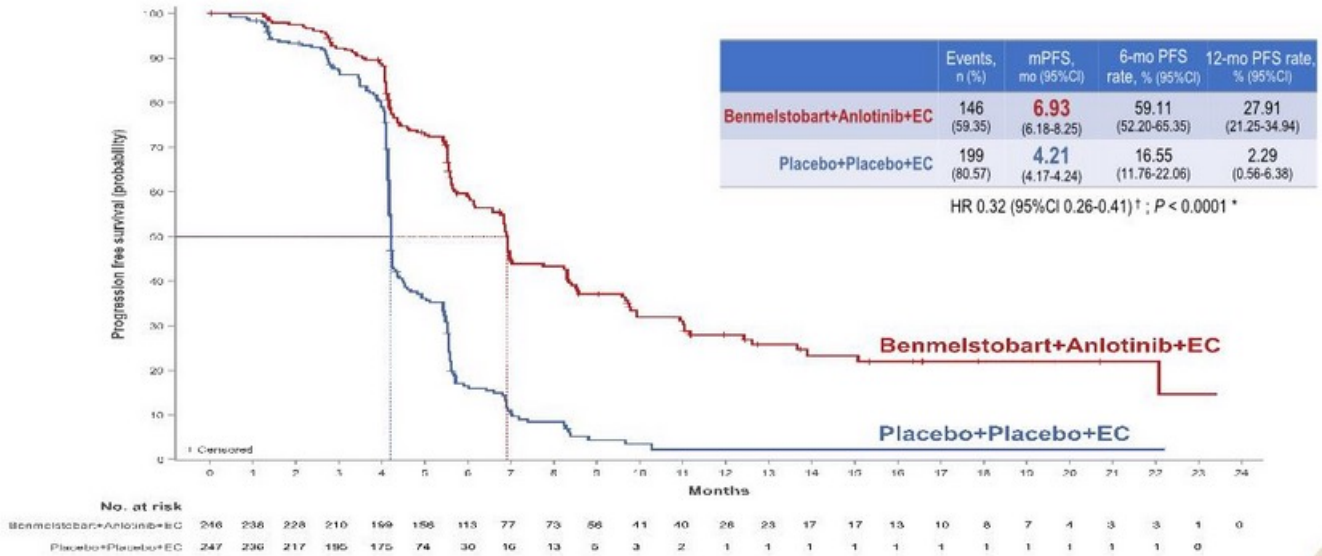
DeLLphi-304 (NCT05740566): Tarlatamab vs. SoC in relapsed SCLC



Primary endpoint
- OS

Secondary endpoints
- PFS, PRO

VEGF still holding on?



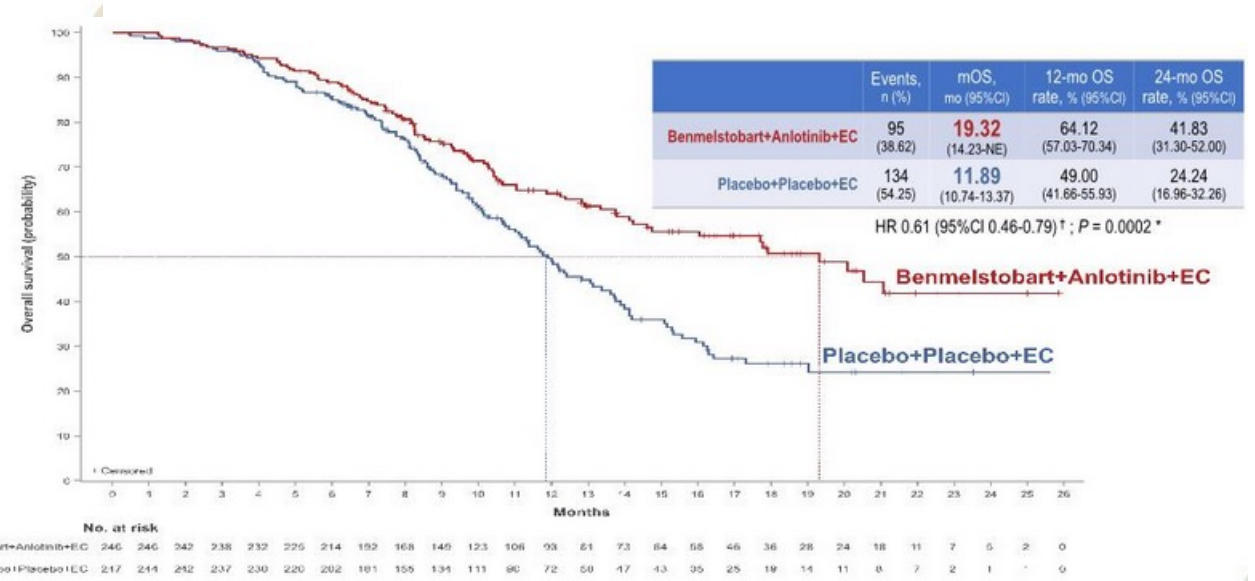
	Events, n (%)	mPFS, mo (95%CI)	6-mo PFS rate, % (95%CI)	12-mo PFS rate, % (95%CI)
Benmelstobart+Anlotinib+EC	146 (59.35)	6.93 (6.18-8.25)	59.11 (52.20-65.35)	27.91 (21.25-34.94)
Placebo+Placebo+EC	199 (80.57)	4.21 (4.17-4.24)	16.55 (11.76-22.06)	2.29 (0.56-6.38)

HR 0.32 (95%CI 0.26-0.41)† ; *P* < 0.0001 *

Investigational Regimen:

Benmelstobart + Anlotinib + Platinum + Etoposide

- Anti-PD-1
- TKI against VEGF, FGFR, PDGFR, c-kit
- Control arm



	Events, n (%)	mOS, mo (95%CI)	12-mo OS rate, % (95%CI)	24-mo OS rate, % (95%CI)
Benmelstobart+Anlotinib+EC	95 (38.62)	19.32 (14.23-NE)	64.12 (57.03-70.34)	41.83 (31.30-52.00)
Placebo+Placebo+EC	134 (54.25)	11.89 (10.74-13.37)	49.00 (41.66-55.93)	24.24 (16.96-32.26)

HR 0.61 (95%CI 0.46-0.79)† ; *P* = 0.0002 *

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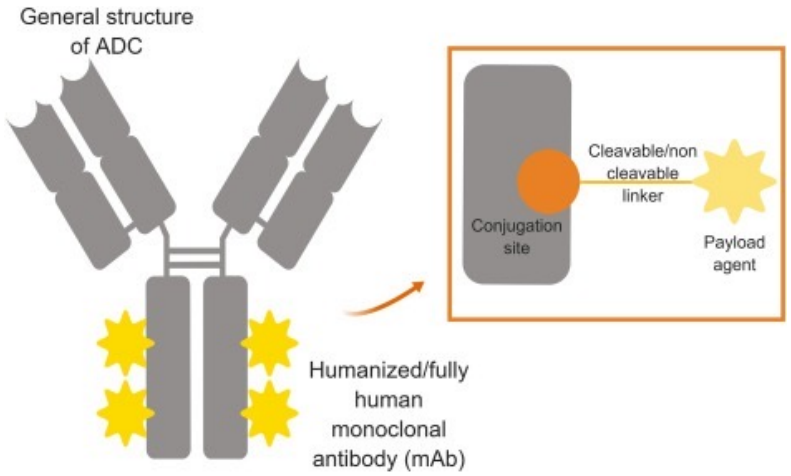
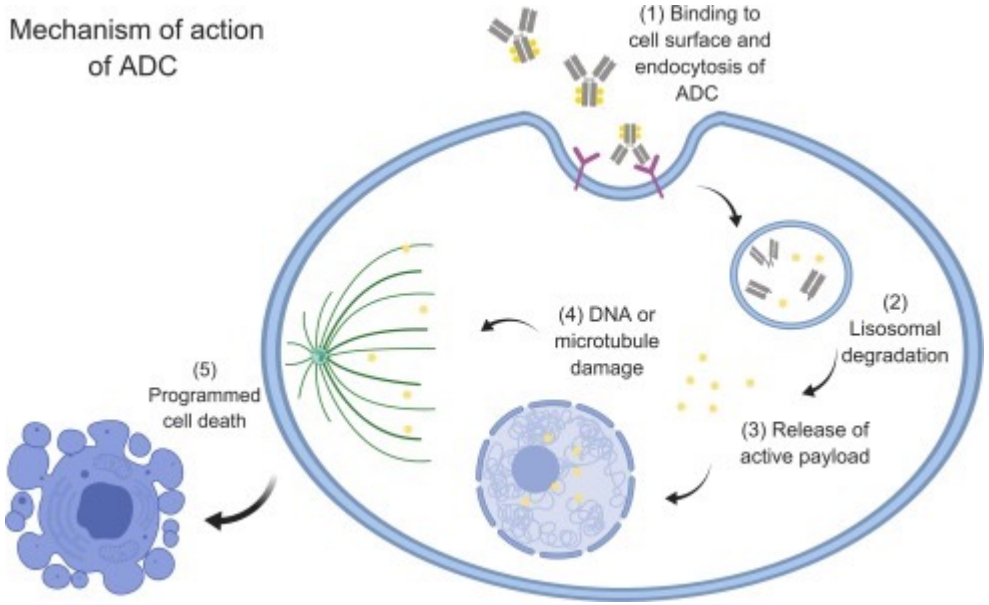
Cheng et al WCLC 2023

ADCs in SCLC

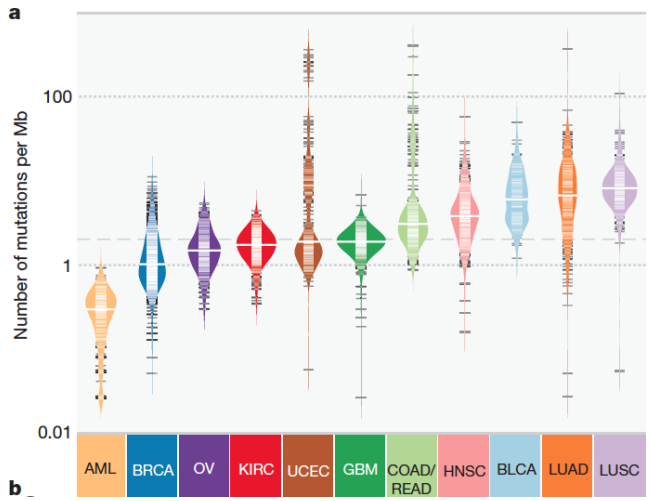
- DLL3
  - RovaT discontinued
- TROP2
  - IMMU-132
- B7-H3
  - DS-7300 (I-DXD)
- SEZ6
  - ABBV-011, -706





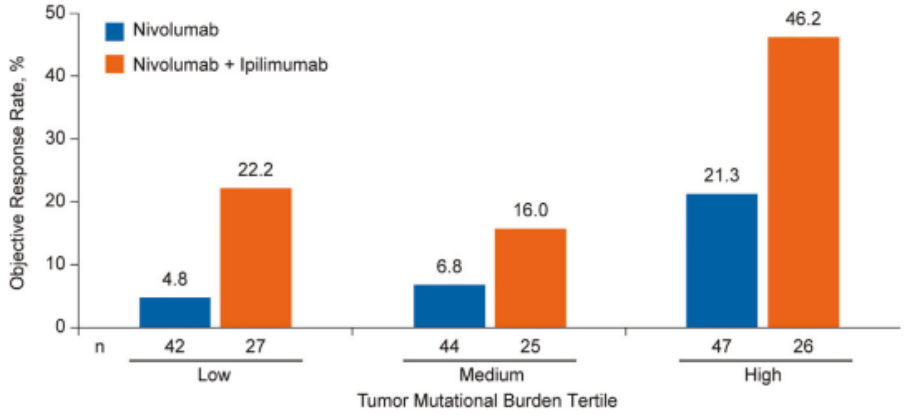
Ricciuti, B, et al, Sem Cancer Biol 2021, 69:268-278

Search for immunotherapy biomarkers is Ongoing in SCLC



Tumor Mutational Burden: A potential biomarker?

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

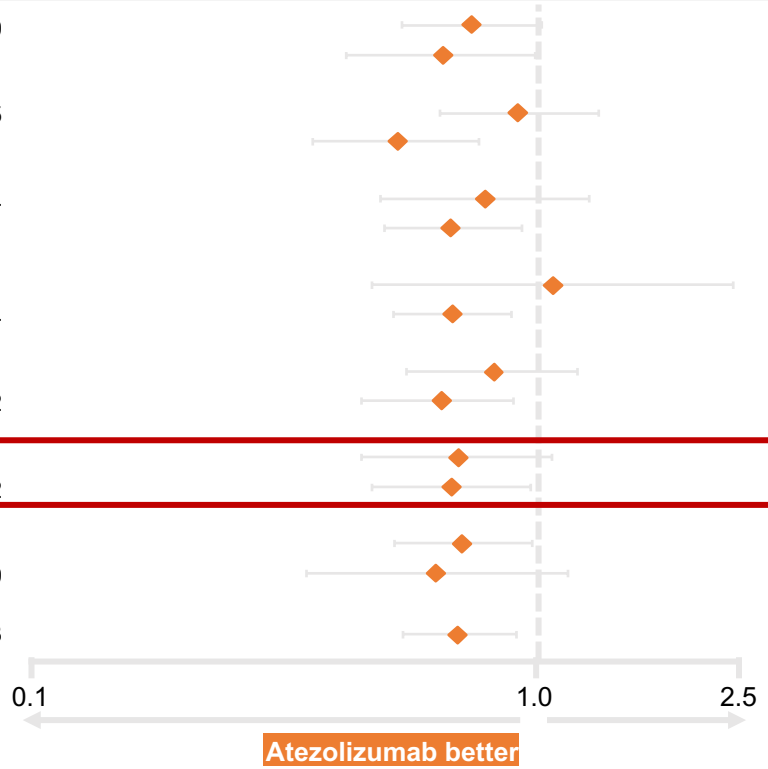


CM032: high TMB cohort- RR 46.2 % and 1YOS 62.4 % with ipi/nivo

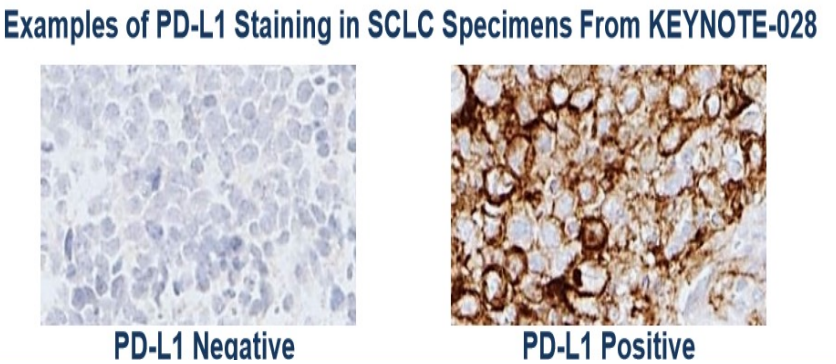
Hellmann, Cancer Cell 2018

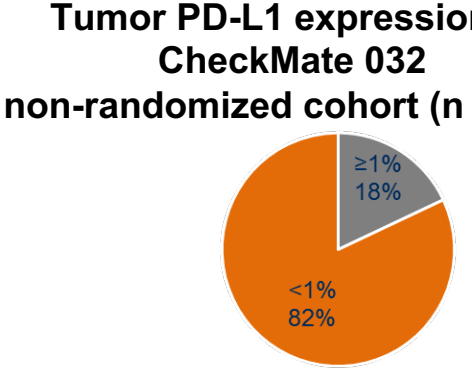
TMB is not predictive of benefit from atezo + chemotherapy

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





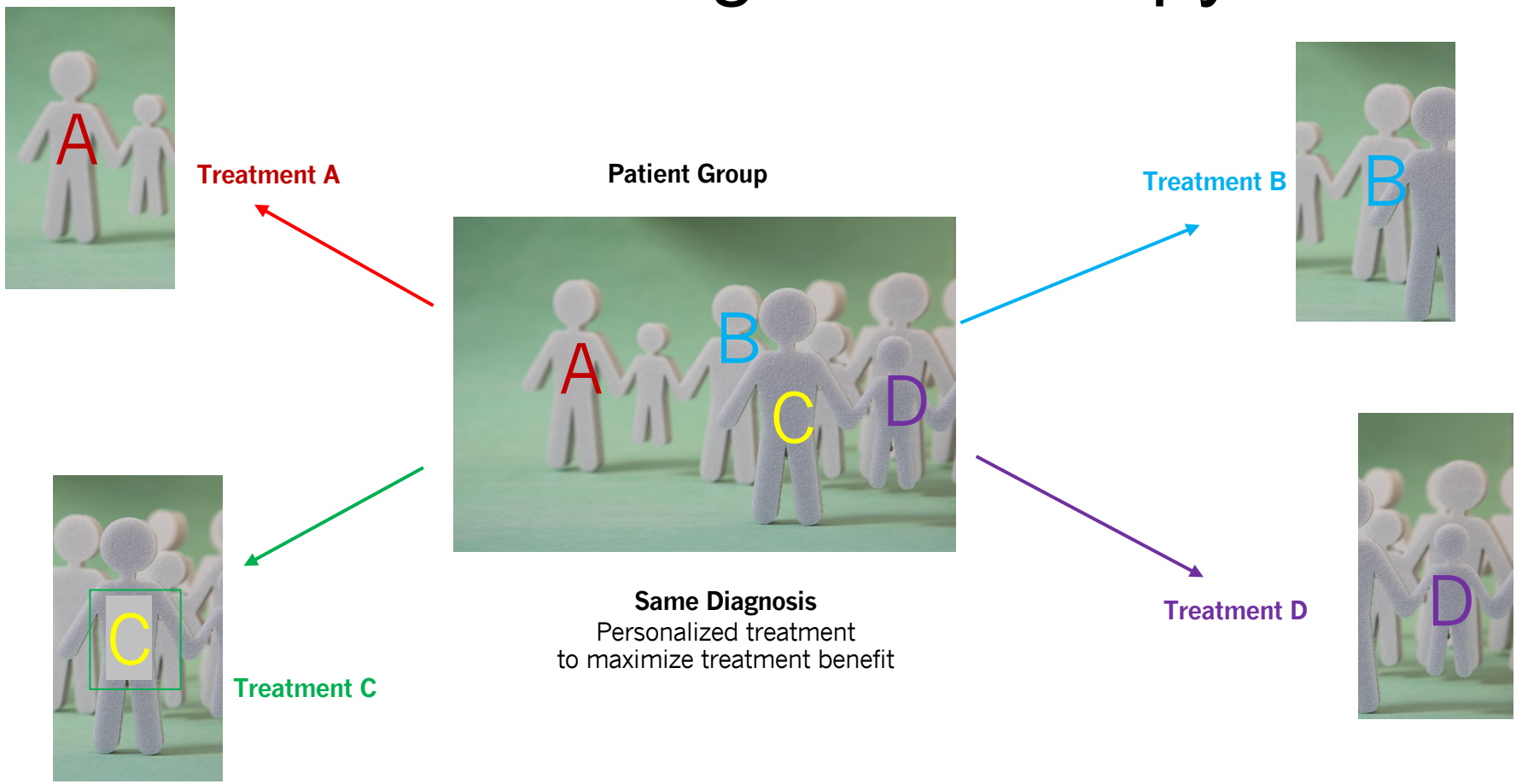
- PD-L1 combined score = ratio of PD-L1 positive cells (including tumor cells, lymphocytes and macrophages) to the total number of tumor cells
- Phase 2 KN-028 trial of pembro in SCLC showed that 39% of patients were PD-L1 positive (≥ 1)
- PD-L1 positivity predicted for higher response 35.7% vs 6% and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

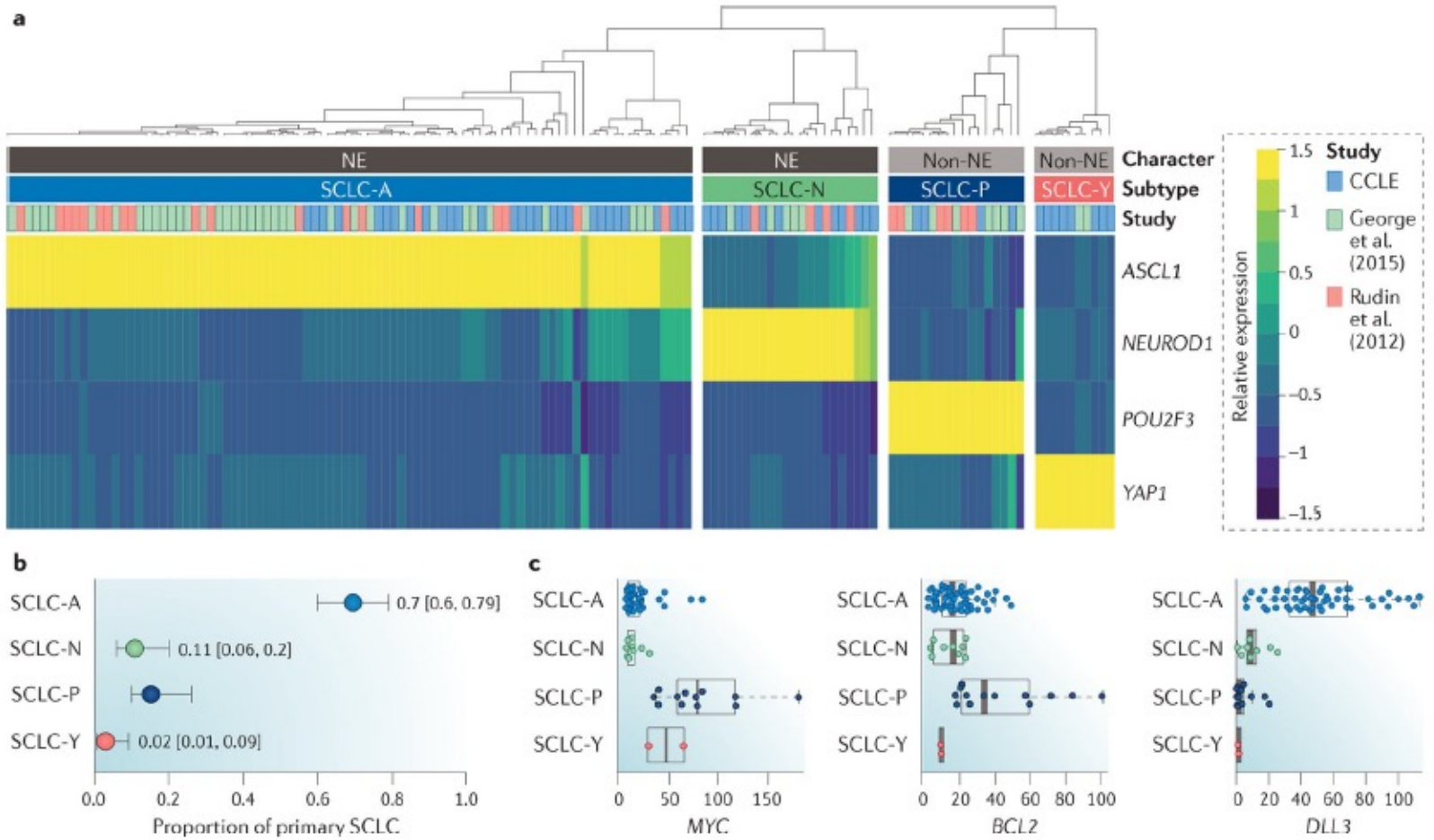
Ott, et al, WCLC 2015, Chung HC, et al. ASCO 2018

The Promise of Personalized Medicine and Targeted Therapy



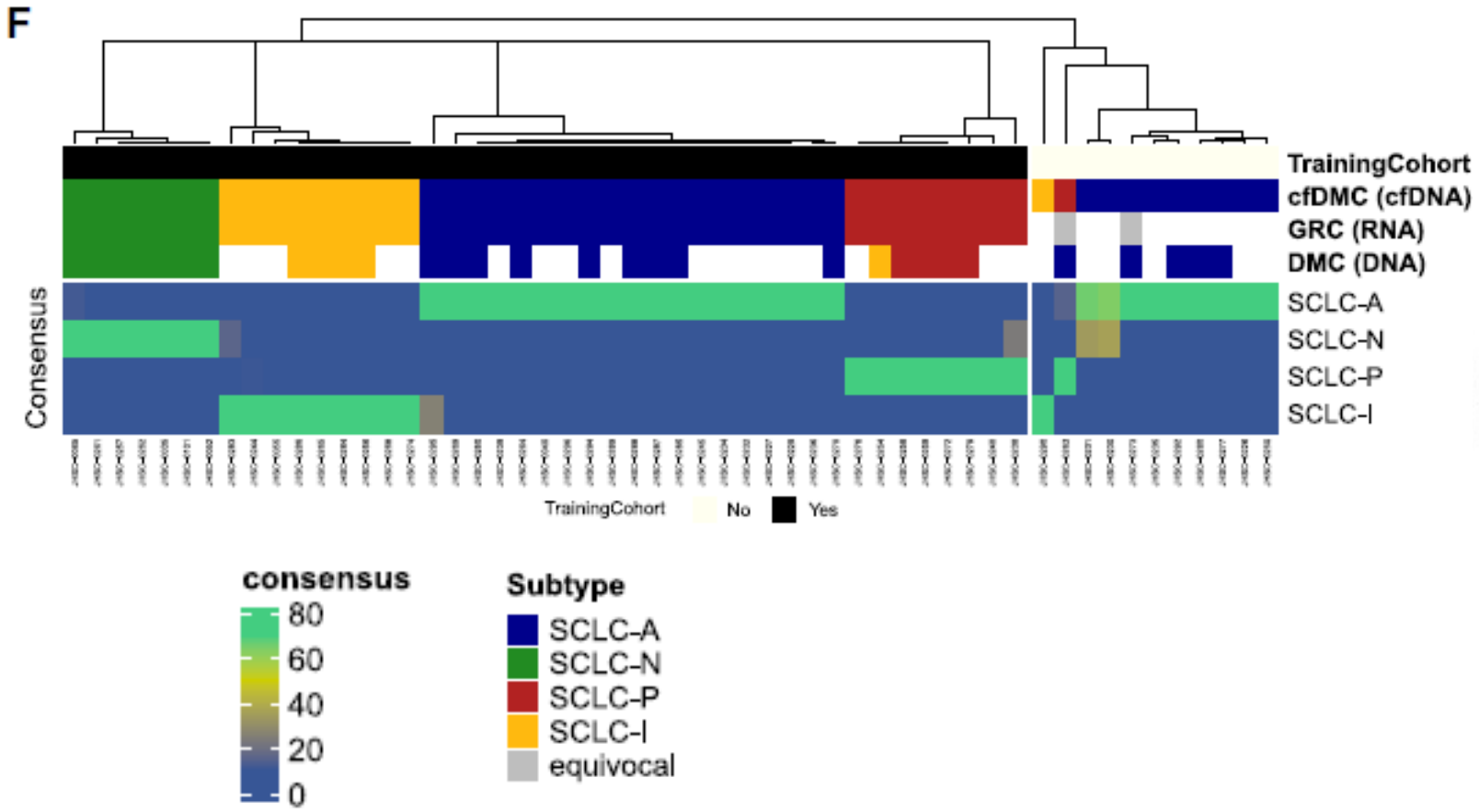
- Image courtesy of Djem and Shutterstock.com.

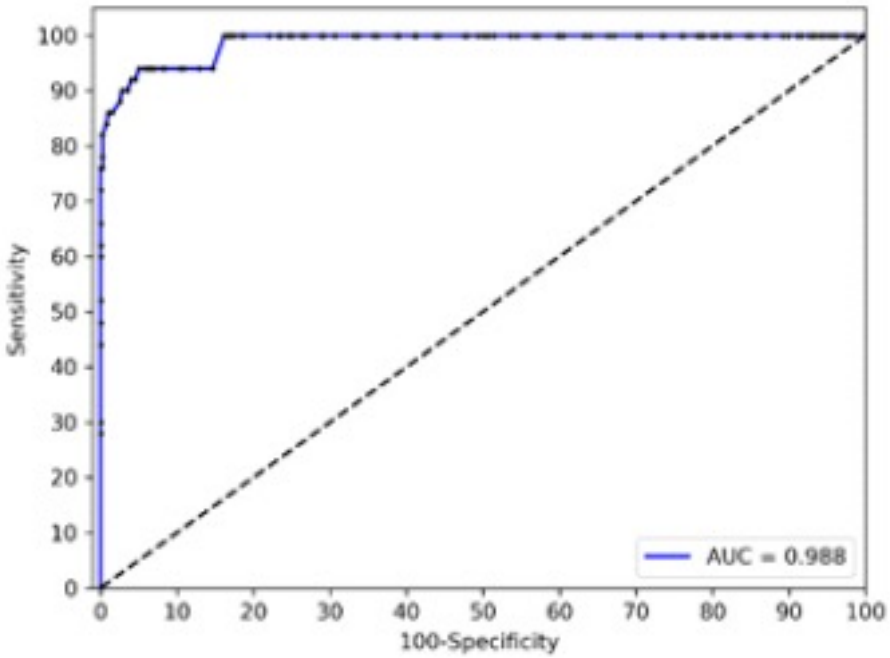
SCLC Biology: Molecular Subtypes by Expression of Key Transcriptional Regulators



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

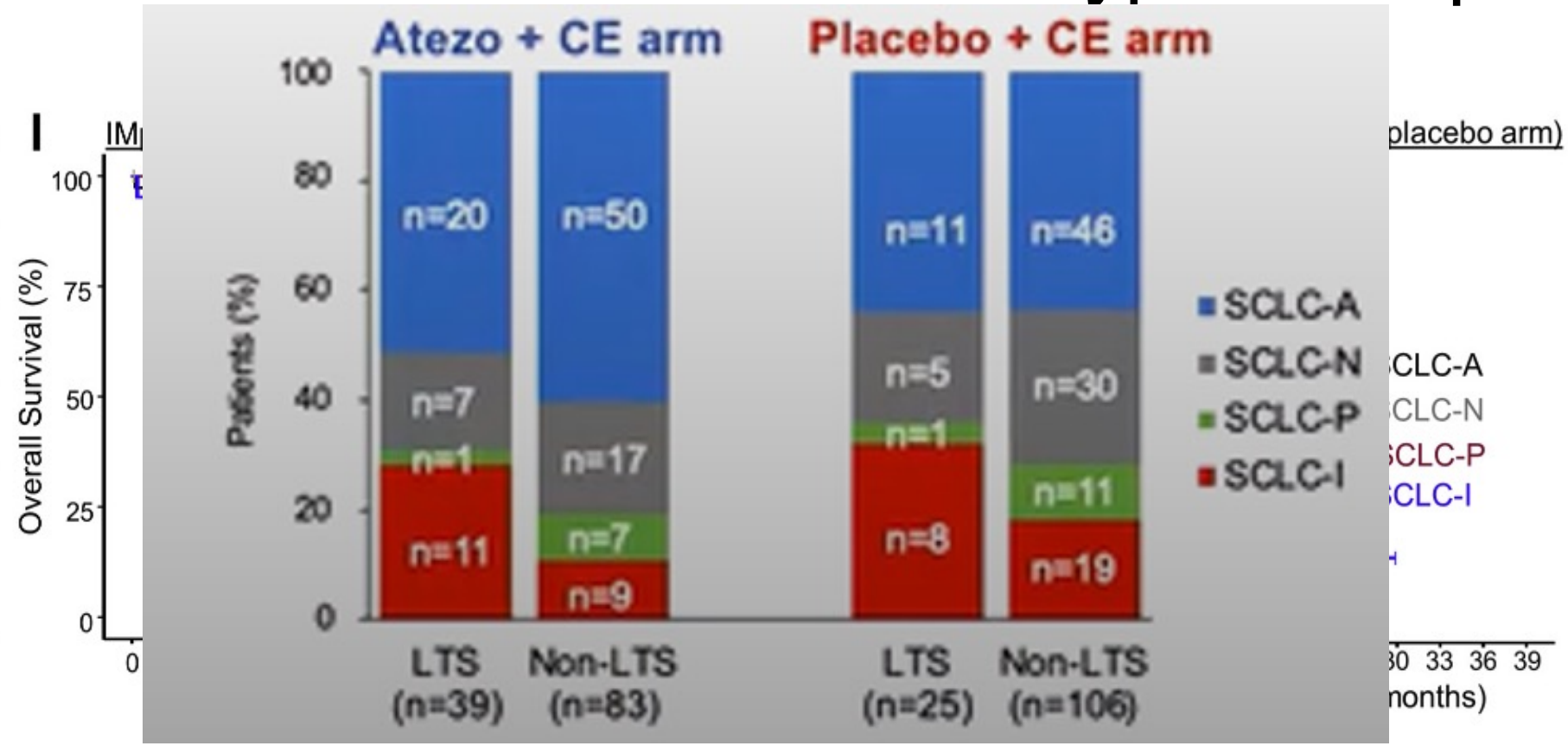
Subtyping using plasma:





Heeke Cancer Cell 2024

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



Gay, et al. Cancer Cell 2021; Liu et al. ESMO Virtual Plenary 2021

SCLC: Key Points

- ChemoIO combinations are standard 1L regimens
  - Long term data from CASPIAN and IMpower133/Imbrella A shows potential for durable response in 1L
- Lurbinectidin as a viable 2nd line agent, but much to be desired.
- DLL3 as a target: furthest along is Tarlatamab-BiTE- can have durable efficacy!
- ADCs with promising activity but durability in question..
- Validated biomarkers (as always) would be nice!
- Understanding the complexity and biology of SCLC may lead to more effective treatments

Questions?