SCLC - the new frontier in treatment

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- **T1-2 N0-1 M0:**
  - Surgery + four cycles of adjuvant CT and POR if staged pN1 or pN2
  - concurrent CT and thoracic RT
- **All other patients with T1-4, N0-3 M0 in a good PS**
  - concurrent CT and thoracic RT
  - thoracic RT initiated with the first or second cycle (i.e. within 30 days) of CT
- **All patients with T1-4, N0-3 M0 disease without disease progression after treatment and a reasonably good PS should be offered PCI**
- **First-line treatment of metastatic disease**
  - 4-6 cycles of etoposide plus cisplatin or carboplatin
  - addition of atezolizumab to chemotherapy if no CI of IO
  - Pts in a reasonably good PS with any response to first-line treatment evaluated for PCI
- **Second-line treatment of metastatic disease**
  - Oral or i.v. topotecan recommended for pts having resistant or sensitive relapse
  - CAV being an alternative option
  - Pts with sensitive relapse may derive benefit from reintroduction of the first-line regimen

ES-SCLC Current Management

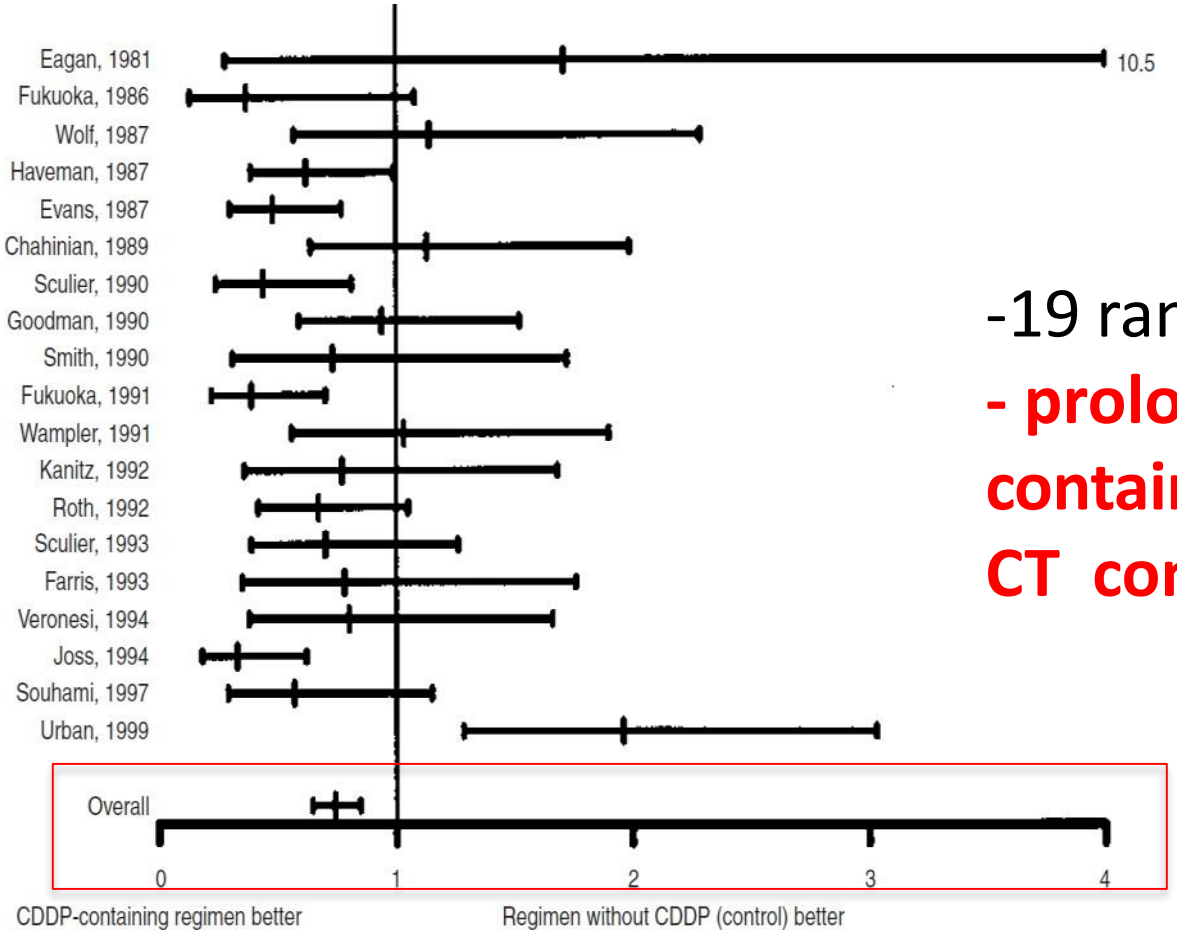
- **Systemic chemotherapy**
  - **Platinum / Etoposide**
  - **Platinum / Irinotecan**

- **PCI**
  - **Lower risk of symptomatic brain metastases (HR 0.27; 95% CI, 0.16 to 0.44; P<0.001)**

- **Thoracic RT**
  - **Secondary analysis, 2-year overall survival was 13% with RT (95% CI 9–19) versus 3% without (95% CI 2–8; p=0·004)**

Noda, NEJM 2002 **Hanna, JCO 2006**
Slotman, NEJM 2007 **Slotman, Lancet 2015**

Adoption of etoposide–cisplatin as a standard treatment regimen till 2019

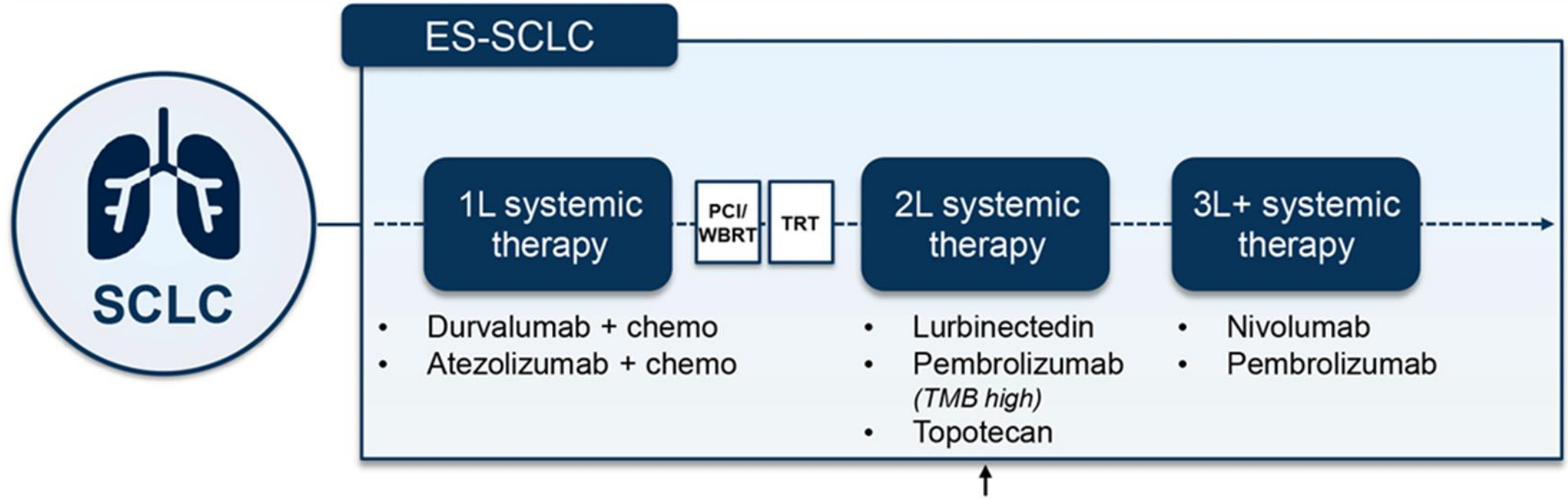


-19 randomised trials (4054 patients)

- prolonged OS of pts receiving a cisplatin-containing regimen compared with older CT combinations

Pujol, JL et al. Br J Cancer 2000

Systemic Treatment Options in ES-SCLC

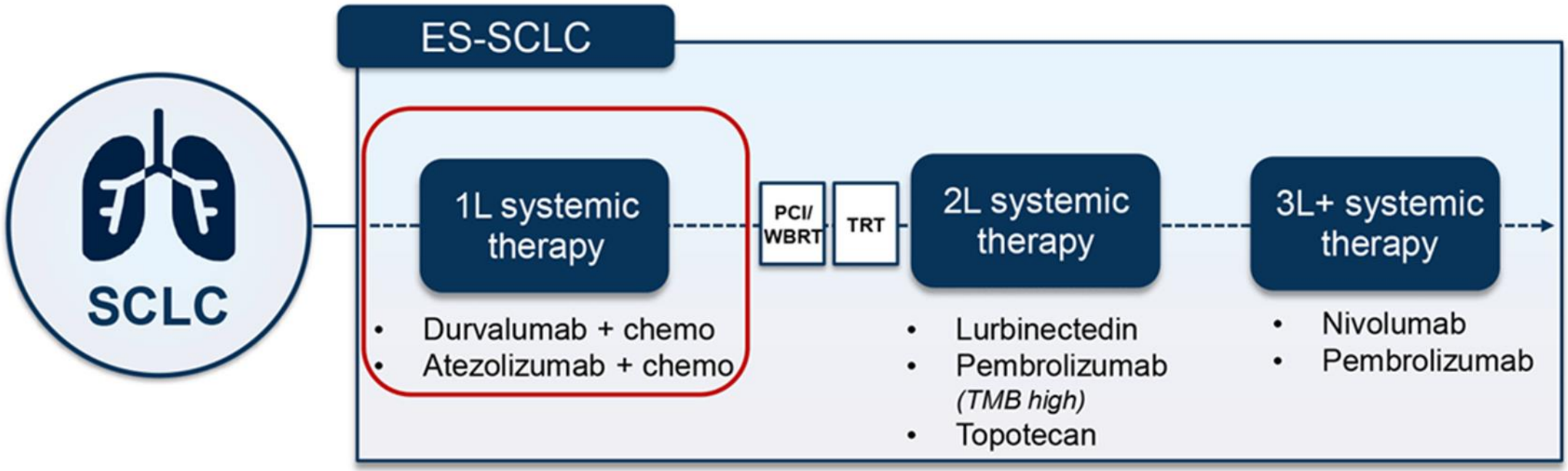


June 15, 2020: FDA granted accelerated approval to **lurbinectedin** for adult patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy[1]

June 16, 2020: FDA granted accelerated approval to **pembrolizumab** for adult and pediatric patients with unresectable or metastatic tumor mutational burden–high (≥10 mut/Mb) solid tumors, as determined by an FDA-approved test, who have progressed following prior treatment and who have no satisfactory alternative treatment options[2]

1. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-lurbinectedin-metastatic-small-cell-lung-cancer.
2. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-pembrolizumab-adults-and-children-tmb-h-solid-tumors.

Selection of First-Line Treatment for ES-SCLC

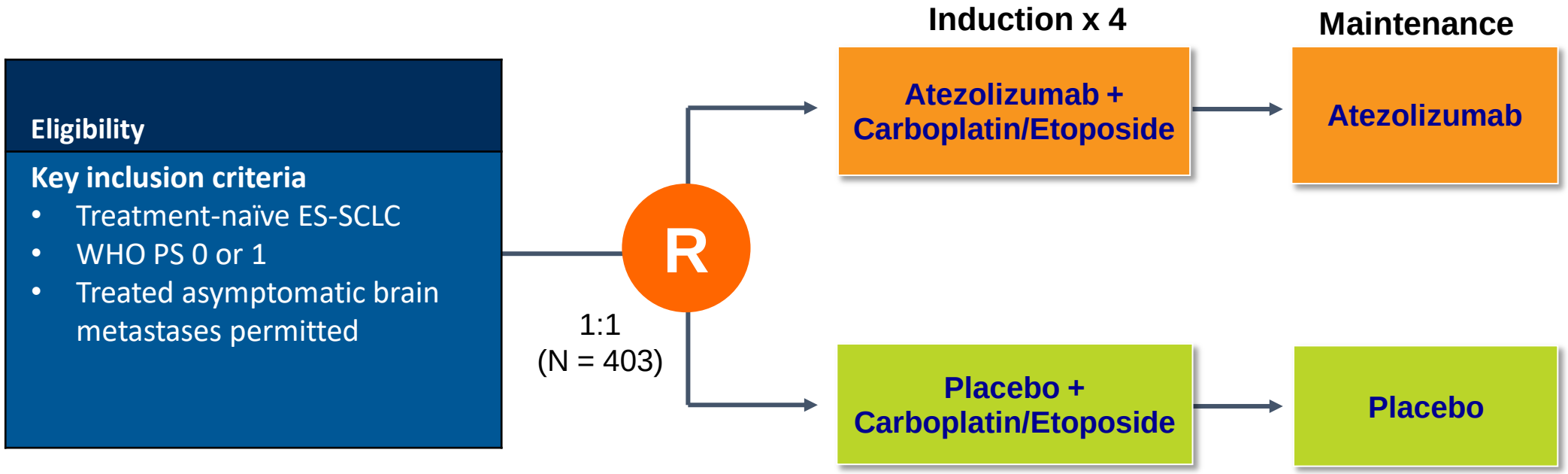


Chemotherapy + Immunotherapy in SCLC: Efficacy Summary

	IMpower133	Caspian D	Caspian D/T	KN-604	EA5161
Median PFS, mo	5.2	5.1	4.9	4.5	5.5
Median OS, mo	12.3	13	10.4	10.8	11.3
12-mo OS	51.7	52.8	43.8	45.1	~48
24-mo OS	~22	22.2	23.4	22.5	NR
HR PFS (95% CI)	0.77 (0.62-0.96)	0.78 (0.65-0.94)	0.84 (0.70-1.01)	0.75 (0.61-0.91)	0.68 (0.48-1.0)
HR OS (95% CI)	0.70 (0.54-0.91)	0.73 (0.59-0.91)	0.82 (0.68-1.00)	0.80 (0.64-0.98)	0.67 (0.46-0.98)

27 June 2019, AstraZeneca announced positive OS results from the Phase III CASPIAN trial with Imfinzi in 1st-line SCLC

IMpower133 Phase III Study Design



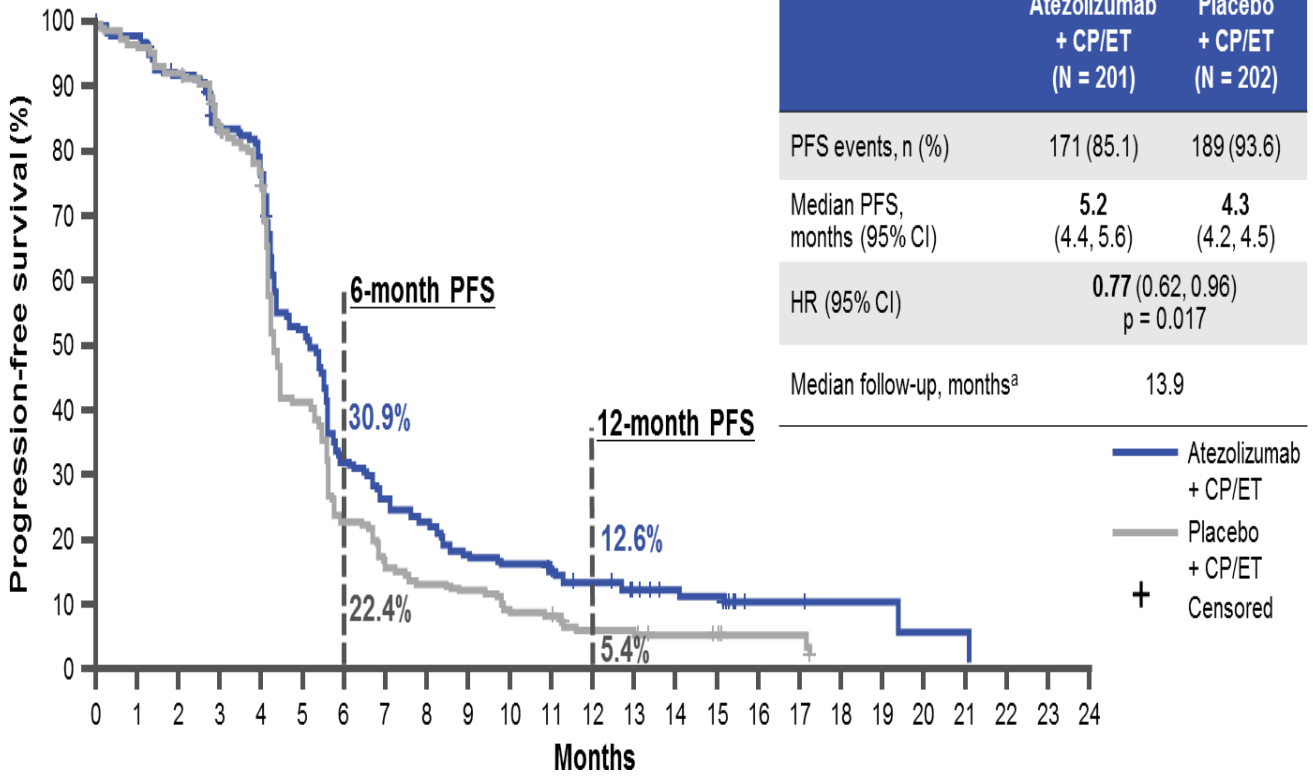
Coprimary endpoints: Overall survival and investigator-assessed PFS
Key secondary endpoints: Objective response rate, duration of response, safety

Liu SV et al. ESMO 2018;Abstract PL02.07.

N Engl J Med 2018; 379:2220-2229 DOI: 10.1056/NEJMoa1809064

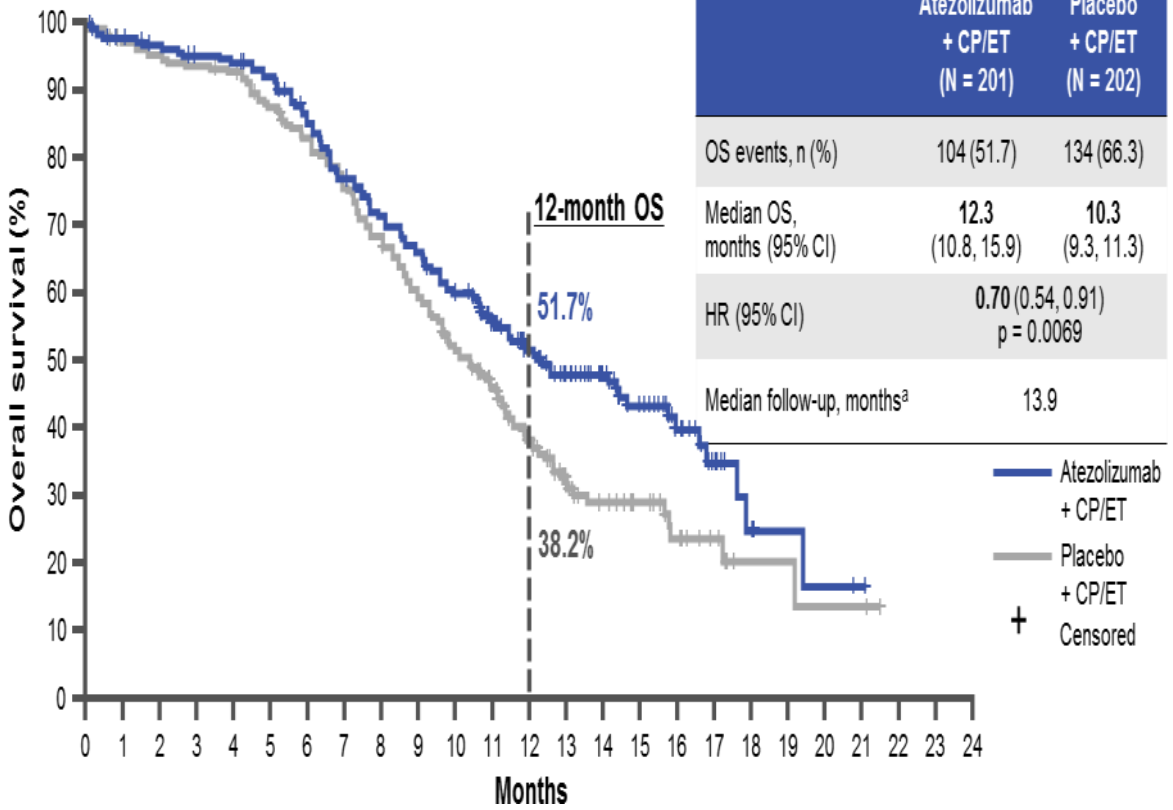
Addition of atezolizumab to chemotherapy resulted in significantly longer OS and PFS

mPFS: 5.2 vs 4.3 mo



	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	

mOS: 12.3vs 10.3 mo

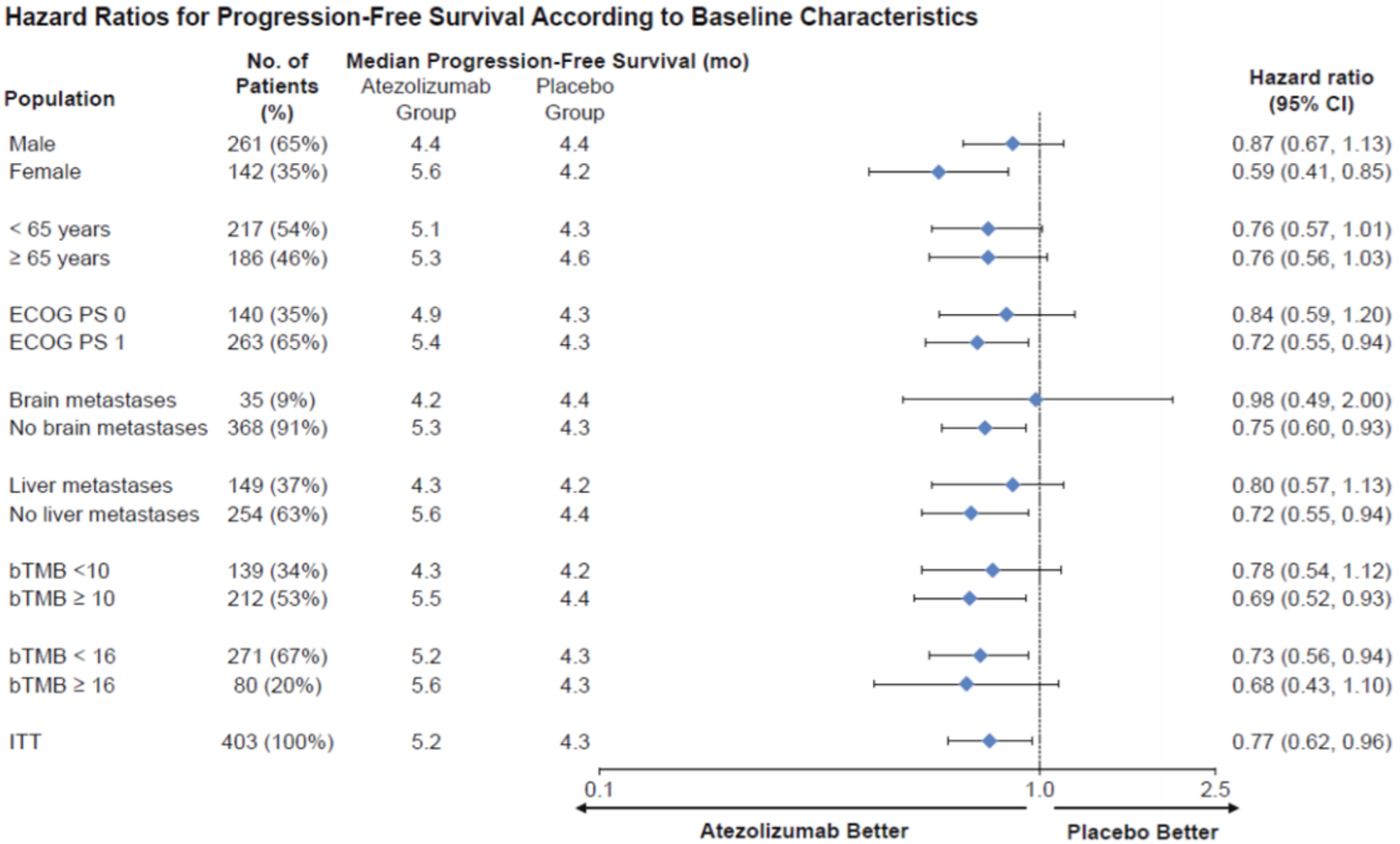


	Atezolizumab + CP/ET (N = 201)	Placebo + CP/ET (N = 202)
OS events, n (%)	104 (51.7)	134 (66.3)
Median OS, months (95% CI)	**12.3** (10.8, 15.9)	**10.3** (9.3, 11.3)
HR (95% CI)	**0.70** (0.54, 0.91) p = 0.0069	
Median follow-up, months[a]	13.9	

A new standard of care 1st line !

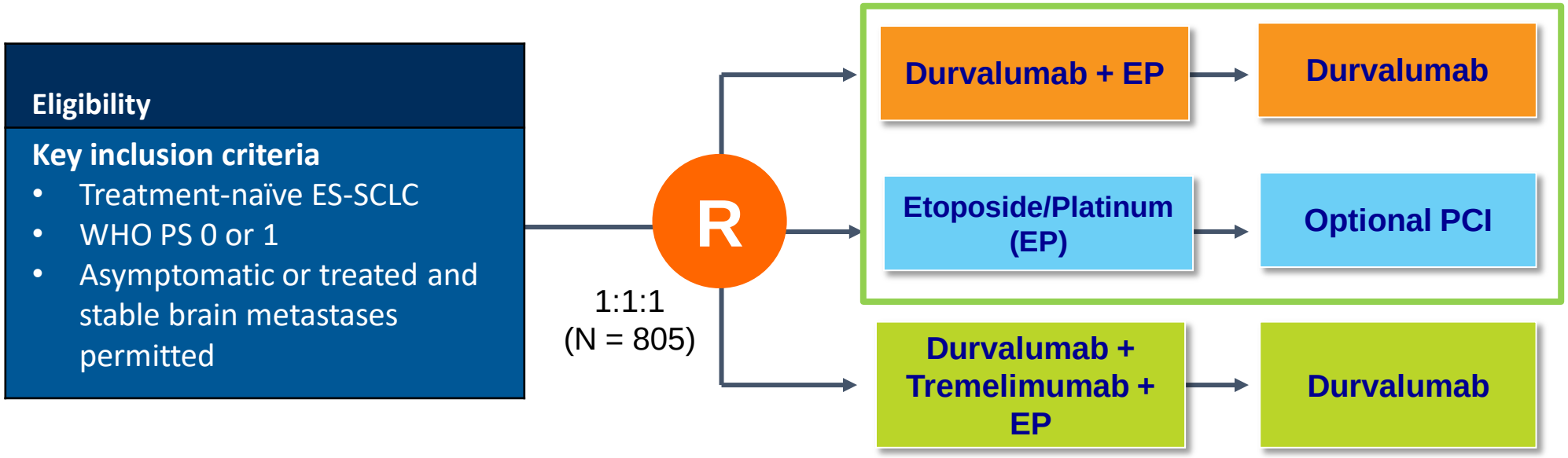
L. Horn et al, NEJM 2018

Figure S2. Subgroup analysis of investigator-assessed progression-free survival according to baseline characteristics.



bTMB, blood tumor mutational burden; ECOG PS, Eastern Cooperative Oncology Group performance status.

CASPIAN Phase III Study Design



The durvalumab + tremelimumab + EP versus EP comparison continues to final analysis

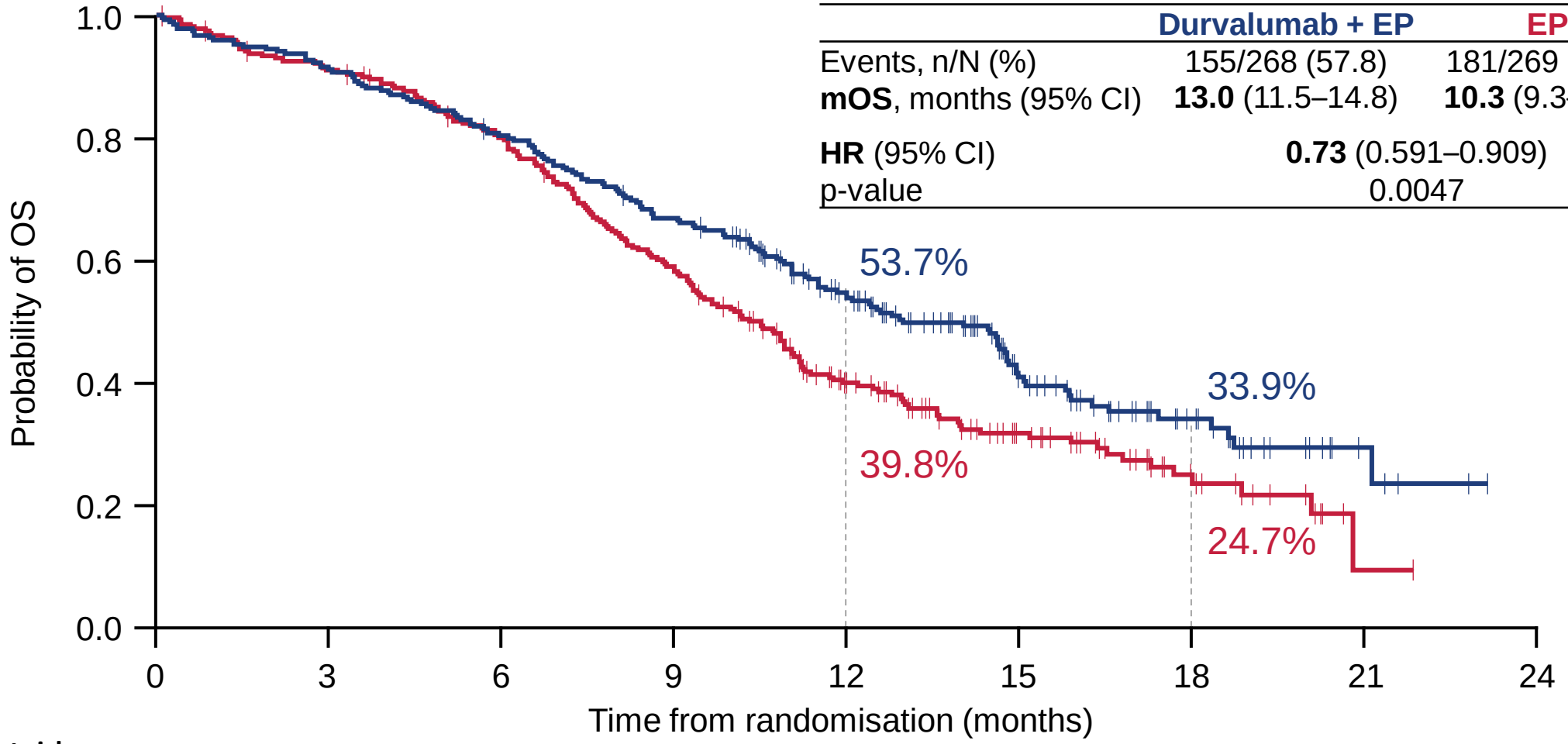
Primary endpoint: Overall survival
Key secondary endpoints: PFS, ORR, safety and tolerability, PROs

Paz-Ares L et al. ESMO 2019;Abstract LBA89.

Lancet 2019; 394: 1940–48 Published Online October 31, 2019 https://doi.org/10.1016/ S0140-6736(19)32597-8

Overall Survival (Primary Endpoint)

	Durvalumab + EP	EP
Events, n/N (%)	155/268 (57.8)	181/269 (67.3)
mOS, months (95% CI)	**13.0** (11.5–14.8)	**10.3** (9.3–11.2)
HR (95% CI)	**0.73** (0.591–0.909)	
p-value	0.0047	

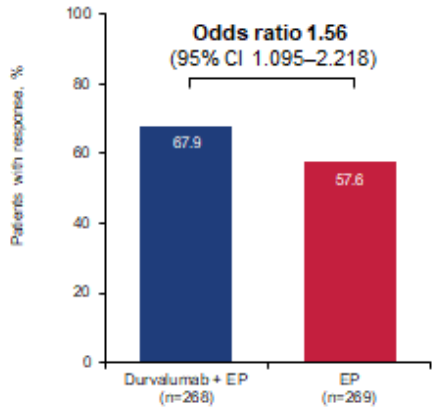


No. at risk								
Durvalumab + EP	268	244	214	177	116	57	25	5	0
EP	269	242	209	153	82	44	17	1	0

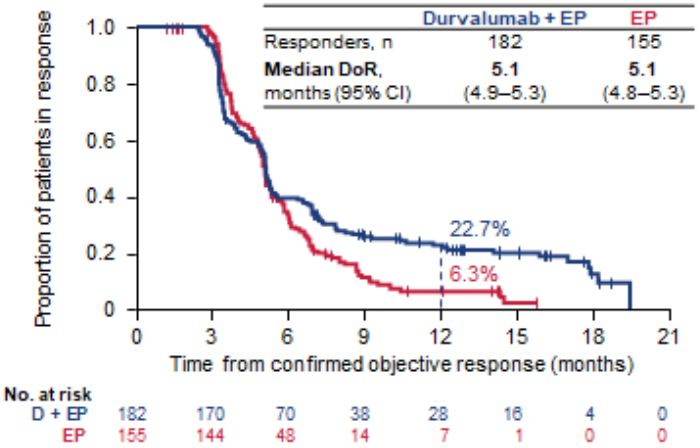
CI, confidence interval;
mOS, median overall survival

Confirmed Objective Response

ORR*



Duration of Response



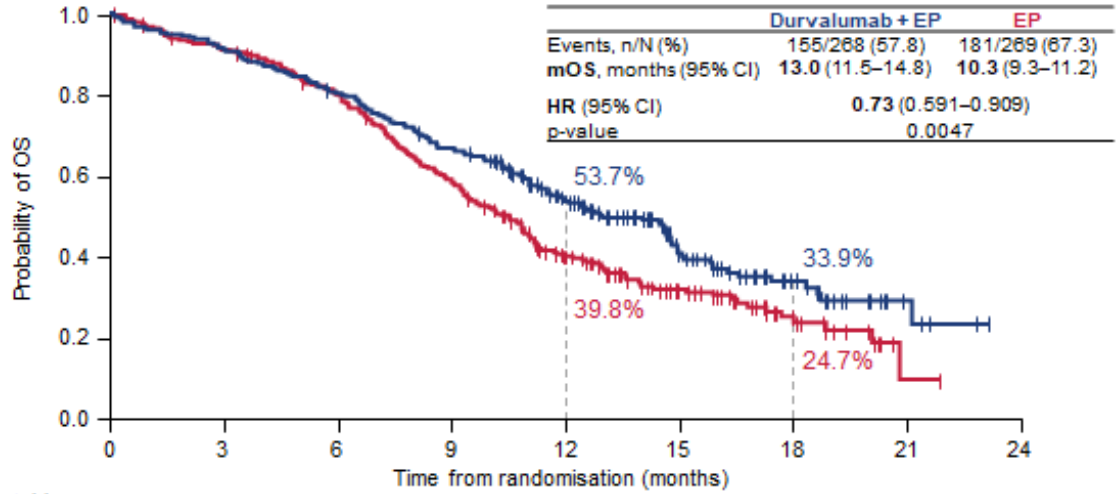
	Durvalumab + EP	EP
Responders, n	182	155
Median DoR, months (95% CI)	**5.1** (4.9–5.3)	**5.1** (4.8–5.3)

No. at risk

D + EP	182	170	70	38	28	16	4	0
EP	155	144	48	14	7	1	0	0

*Investigator assessed per RECIST v1.1

Overall Survival (Primary Endpoint)



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p-value	0.0047	

No. at risk

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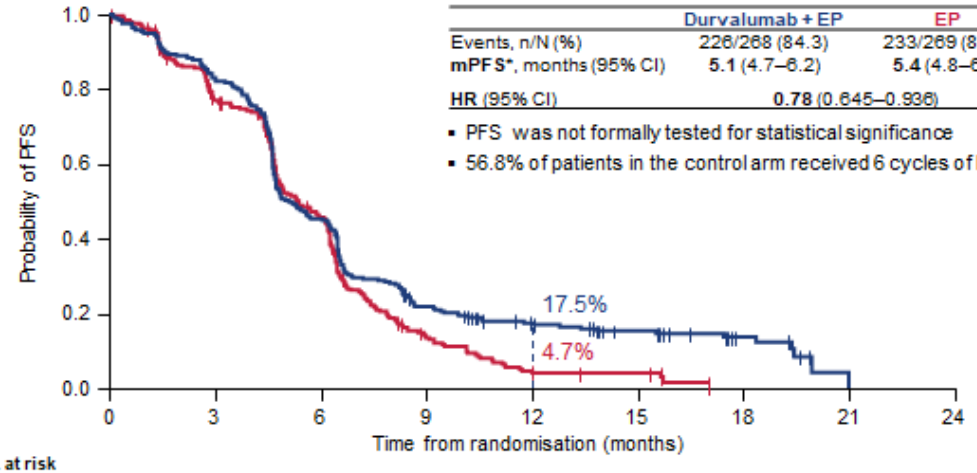
Progression-free Survival



	Durvalumab + EP	EP
Events, n/N (%)	226/268 (84.3)	233/269 (86.6)
mPFS*, months (95% CI)	**5.1** (4.7–6.2)	**5.4** (4.8–6.2)
HR (95% CI)	**0.78** (0.645–0.936)	

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

No. at risk

Durvalumab + EP	268	220	119	54	34	22	10	0	0
EP	269	194	109	30	9	7	0	0	0

*Investigator assessed per RECIST v1.1

mPFS, median progression-free survival

A new standard of care 1st line !

FDA-Approved First-Line Chemoimmunotherapy Regimens in ES-SCLC

	IMpower133[1]			
	Carbo/etoposide + atezolizumab (n = 201)	**Carbo/etoposide + placebo (n = 202)**	**HR**	***p*-value**
Median PFS	5.2 mo	4.3 mo	0.77	0.02
Median OS	12.3 mo	10.3 mo	0.70	0.007

	CASPIAN[2]			
	Platinum/etoposide + durvalumab (n = 268)	**Platinum/etoposide + placebo (n = 269)**	**HR**	***p*-value**
Median PFS	5.1 mo	5.4 mo	0.80	Not tested
Median OS	12.9 mo	10.5 mo	0.75	0.0032

[1] Horn L et al. *N Engl J Med* 2018;379(23):2220-9. [2] Paz-Ares LG et al. ASCO 2020;Abstract 9002.

First-line

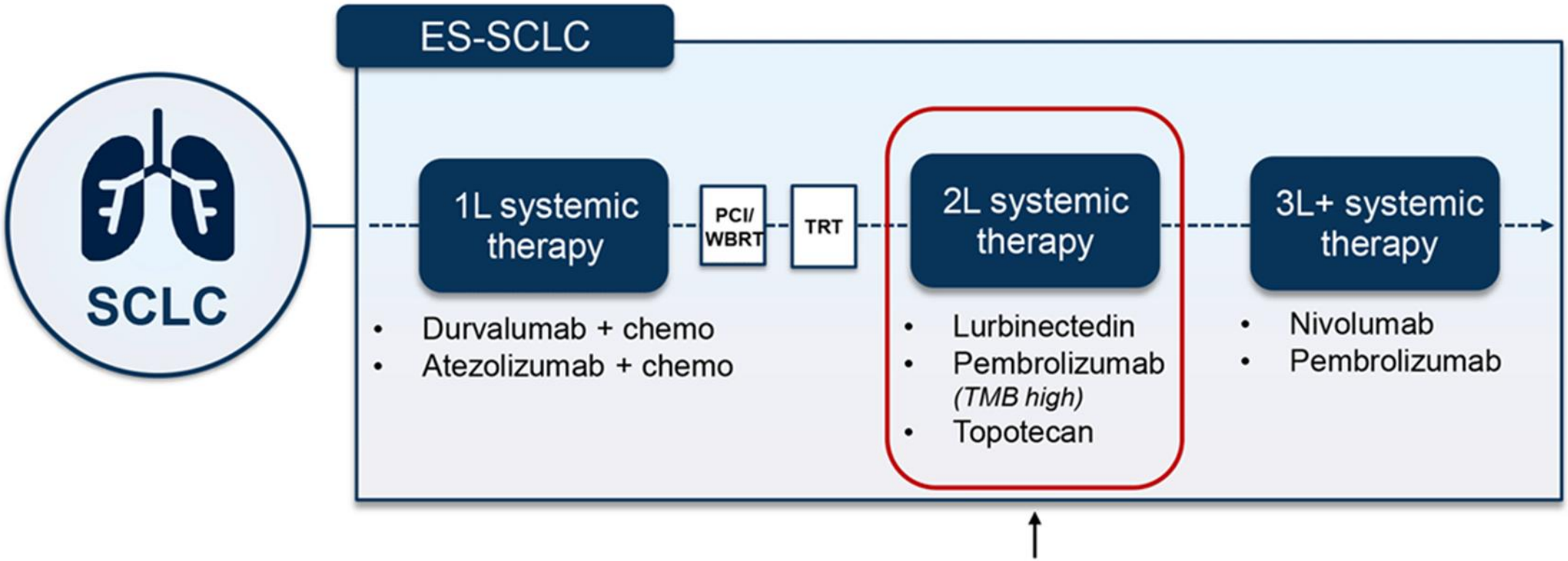
Cisplatin + etoposide 1985

Carboplatin + etoposide 1999

Carboplatin + etoposide + atezolizumab 2019

CT + durvalumab 2020

Case Progression:
Selection of Second-Line Treatment for ES-SCLC



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Case Progression:
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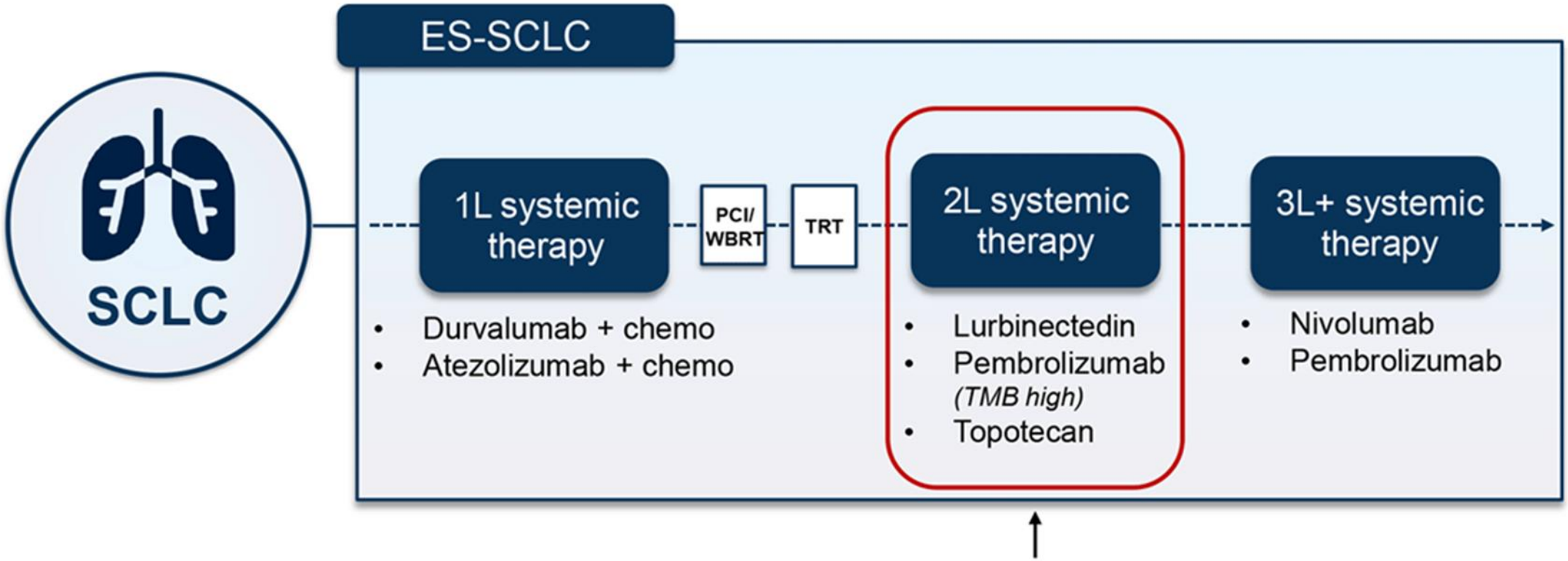

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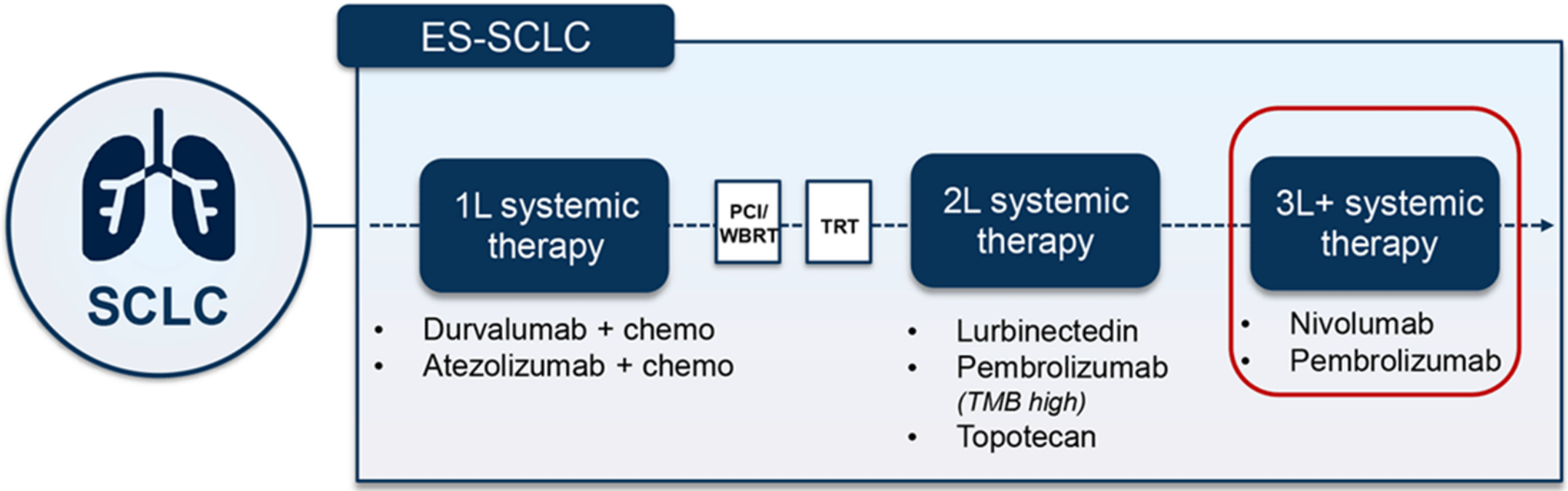
Relasped SCLC: IO trials

Study	N	ORR (%)	mDOR (mo)	mPFS (mo)	OS (mo)	TRAE (G3/4)
KEYNOTE-028 PD-L1(+)	20	33.3 (15.6-55.3)	19.4 (3.6-20+)	1.9	9.7 (4.1 - NR)	
KEYNOTE-158 (all)	107	18.7 (11.8-27.4)	NR (2.1+ - 18.7+)	2.0 (1.0-2.1)	8.7 (5.6-12.0)	12%
PD-L1 (CPS) ≥ 1	42	35.7 (21.6-52.0)		2.1 (2.0-8.1)	14.9 (5.6 - NR)	
PD-L1 (CPS) < 1	50	6.0 (1.3-16.5)		1.9 (1.6-2.0)	5.9 (3.3-10.1)	
CheckMate-032 (initial)						
Nivo 3mg/kg q2	98	10 (5-18)	NR (4.4-NR)	1.4 (1.4-1.9)	4.4 (3.0-0.3)	12%
Nivo 1+ Ipi3	61	23 (13-36)	7.7 (4.0-NR)	2.6 (1.4-4.1)	7.7 (3.6-18.0)	37%*
Nivo3 + Ipi1	54	19 (9-31)	4.4 (3.7-NR)	1.4 (1.2-2.2)	6.0 (3.6-11.0)	

Ott et al., J Clin Oncol 2017; Chung AACR Meeting 2019; Antonia Lancet Oncology 2017; Hellmann ASCO Meeting 2017

Case Progression:
Selection of Third-Line Treatment for ES-SCLC

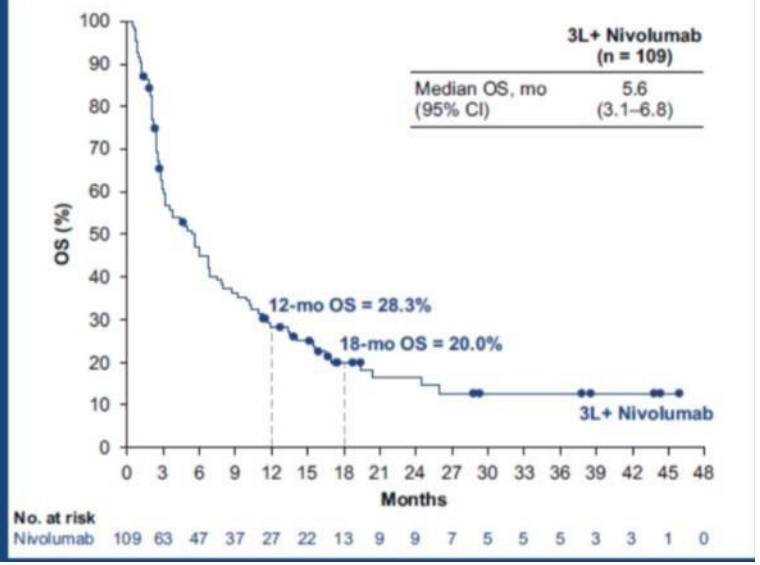


SCLC 3rd line setting: CheckMate 032

ORR: 13%

Table 2. ORRs with Third-or Later-Line Nivolumab Monotherapy

Endpoint	Third-or Later-Line Nivolumab (n = 109)
ORR by BICR[a]	
No. of patients	13
% of patients (95% CI)	11.9 (6.5-19.5)
Best overall response, n (%)	
Complete response	1 (0.9)
Partial response	12 (11.0)
Stable disease	25 (22.9)
Progressive disease	56 (51.4)
Unable to determine	14 (12.8)
Not reported	1 (0.9)
Median time to response, mo	1.6
Duration of response	
≥6 mo, n (%)	10 (76.9)
≥12 mo, n (%)	8 (61.5)
Median (95% CI), mo[b]	17.9 (7.9-42.0)
Range, mo	3.0-42.1



Ready et al, JTO 2018

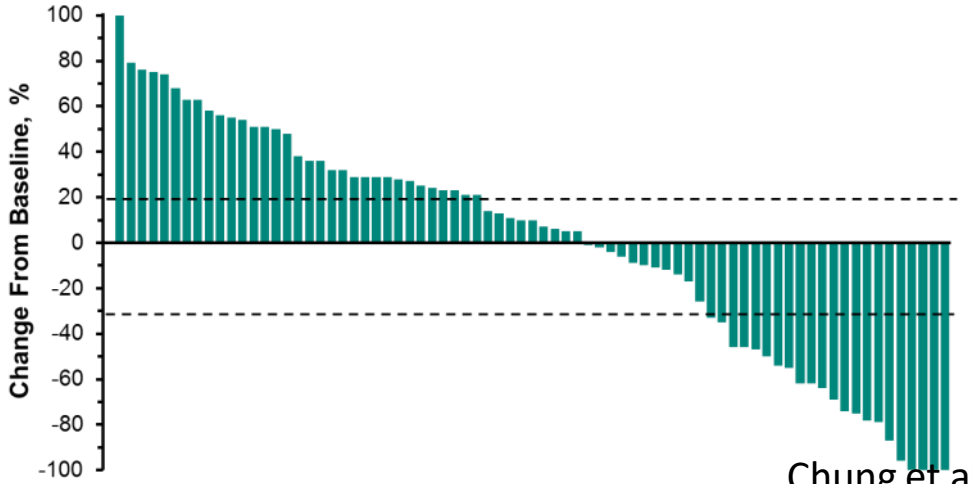
KEYNOTE-028 and KEYNOTE-158: Pembrolizumab After 2 or More Lines

Antitumor Activity (RECIST v1.1 by Independent Review[a])

	Patients N = 83
ORR, n (%; 95% CI)	16 (19.3; 11.4–29.4)
Best overall response,[b] n (%)	
Complete response	2 (2)
Partial response	14 (17)
Stable disease	15 (18)
Noncomplete/partial response[c]	1 (1)
Progressive disease	45 (54)
No assessment[d]	6 (7)

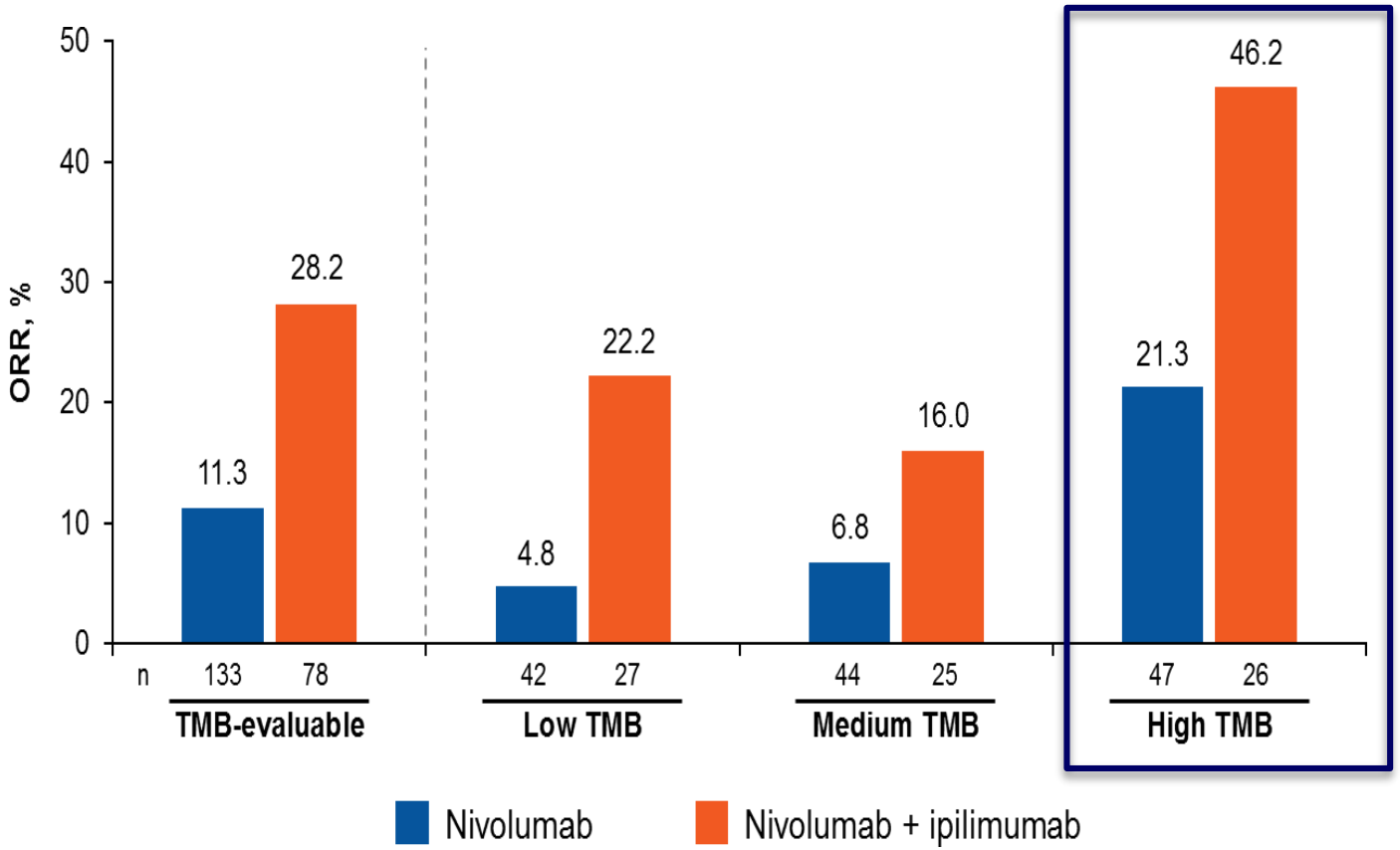
ORR: 16%

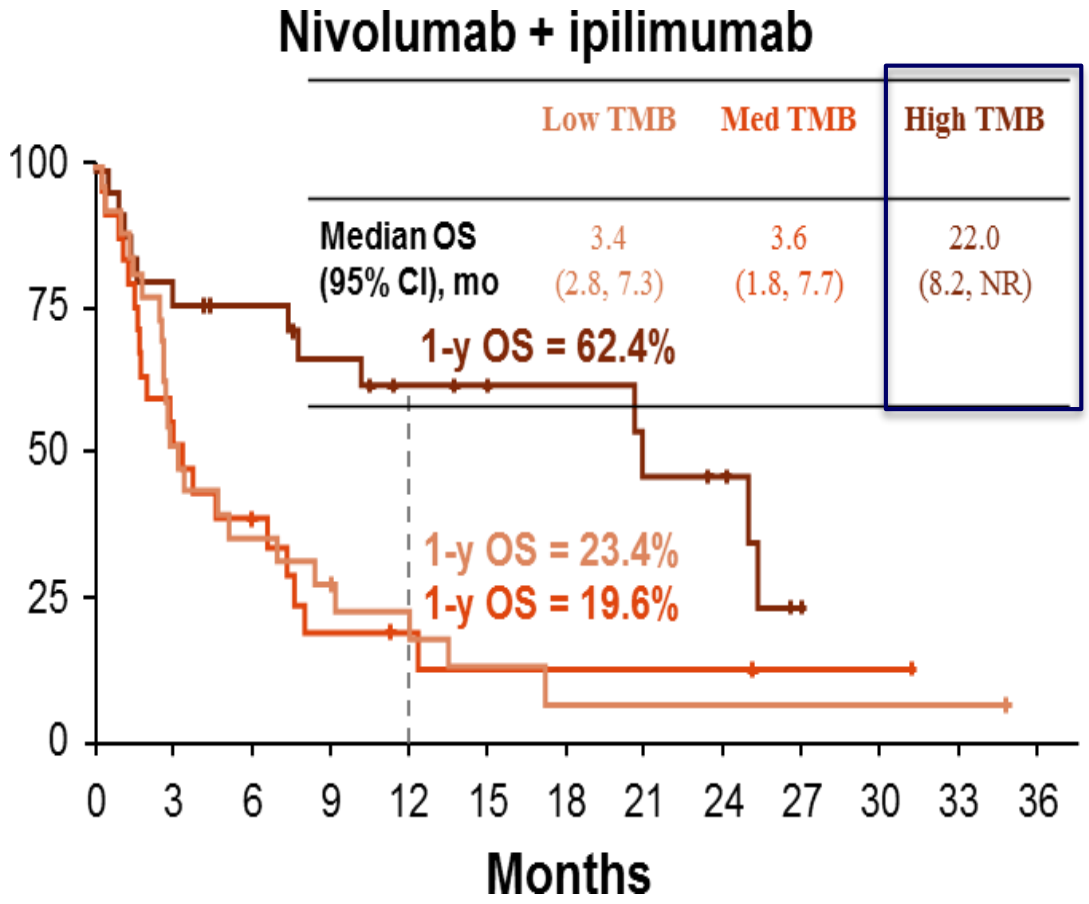
Best Response Change From Baseline in Tumor Size (RECIST v1.1 by Independent Review)



Chung et al, AACR 2019

Impact of TMB on the Efficacy of Nivolumab or Nivolumab + Ipilimumab: An Exploratory Analysis of CheckMate 032





Pts with high TMB had improved ORR, PFS and OS

Impact was greater in ipi/nivo than nivo monotherapy

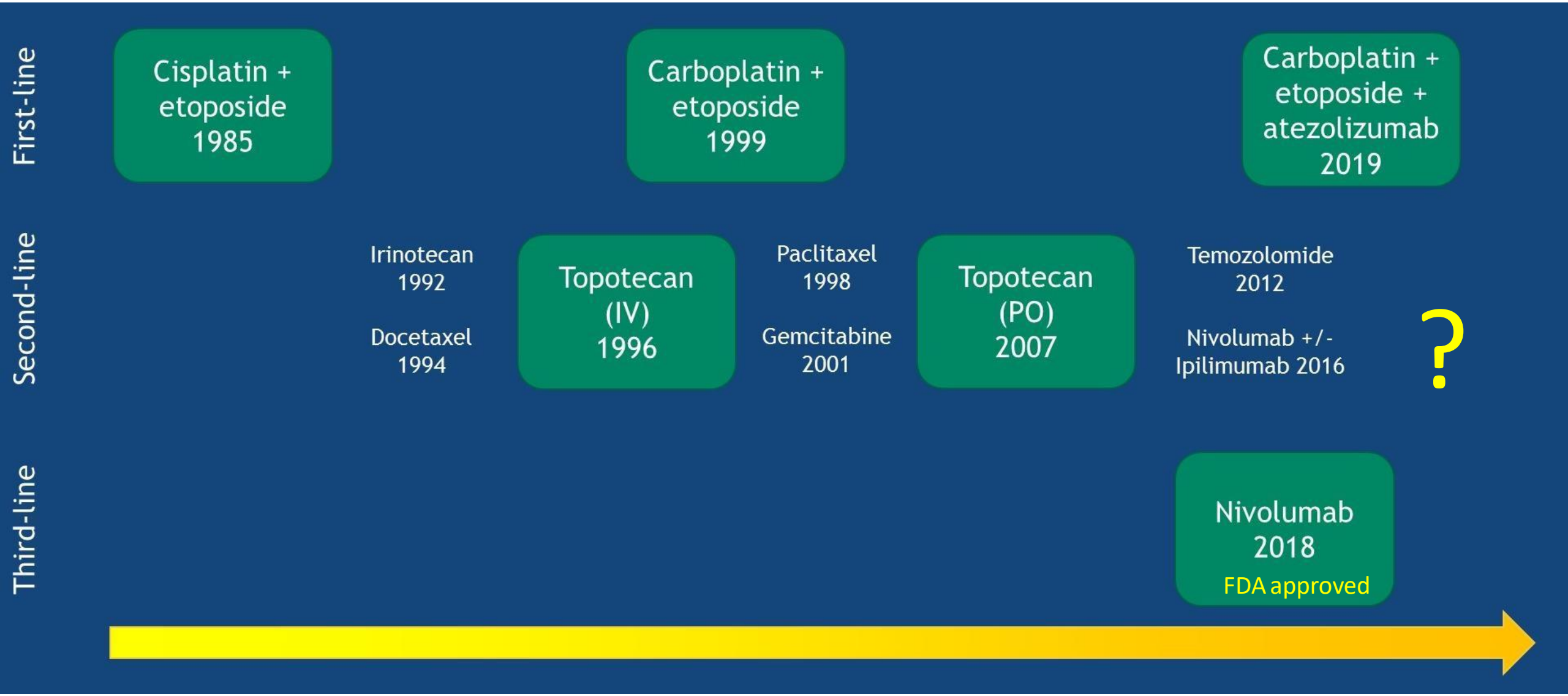
Hellmann et al, cancer cell 2018

Late-Line Immunotherapy Options for ES-SCLC[1-3]

- Nivolumab approved for third-line therapy based on data from CheckMate -032 subgroup:
  - ORR 12% (95% CI, 6.5-19.5)
  - Responses durable for ≥6 mo in 77%, ≥12 mo in 62%, and ≥18 mo in 39% of responding patients

- Pembrolizumab approved for third-line therapy based on KEYNOTE-158 Cohort G and KEYNOTE-028 Cohort C1:
  - ORR was 19% (95% CI, 11-29); CRR 2%
  - Responses were durable for ≥6 in 94%, ≥12 mo in 63%, and ≥18 mo in 56% of responding patients

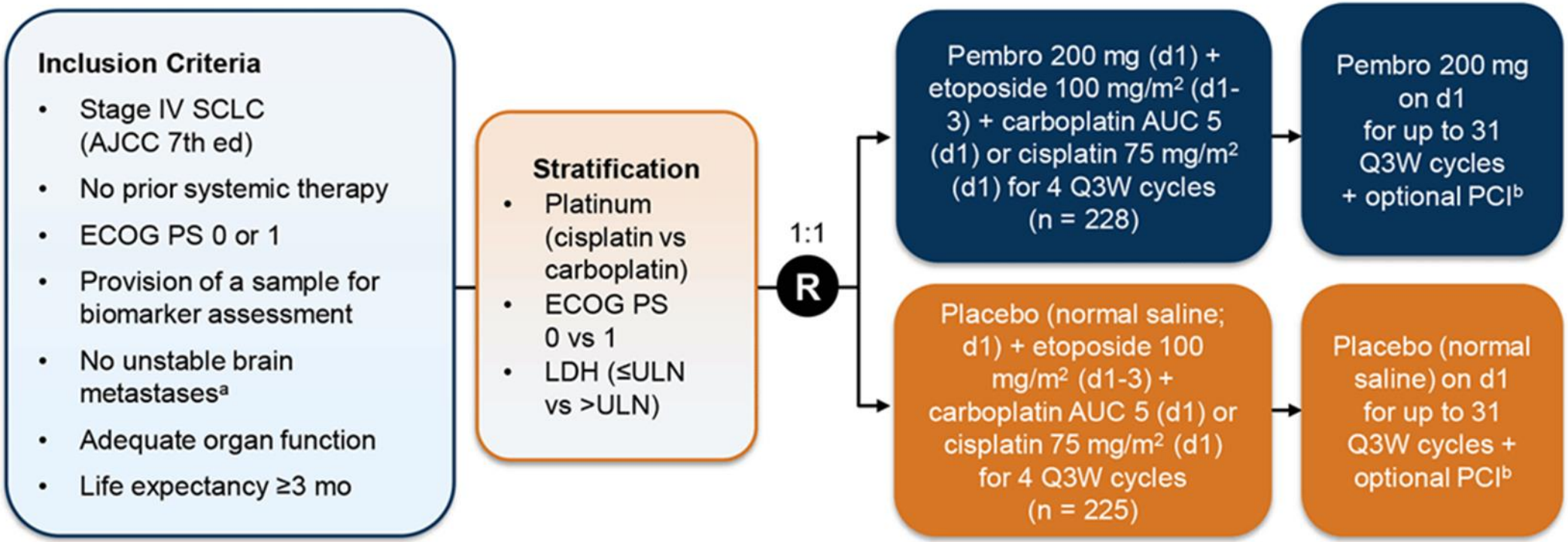
1. Antonia SJ et al. *Lancet Oncol.* 2016;17:883. 2. Chung HC et al. *J Clin Oncol.* 2018;36(suppl 15):8506. 3. Ott PA et al. *J Clin Oncol.* 2017; 35:3823.


First-line
Second-line
Third-line
Cisplatin + etoposide 1985
Carboplatin + etoposide 1999
Carboplatin + etoposide + atezolizumab 2019
Irinotecan 1992
Docetaxel 1994
Topotecan (IV) 1996
Paclitaxel 1998
Gemcitabine 2001
Topotecan (PO) 2007
Temozolomide 2012
Nivolumab +/- Ipilimumab 2016
?
Nivolumab 2018
FDA approved

Selected Highlights From ASCO 2020

What's New and Interesting in SCLC?

KEYNOTE-604: Pembrolizumab or Placebo + Etoposide and Platinum Chemo as 1L Therapy for ES-SCLC[1]

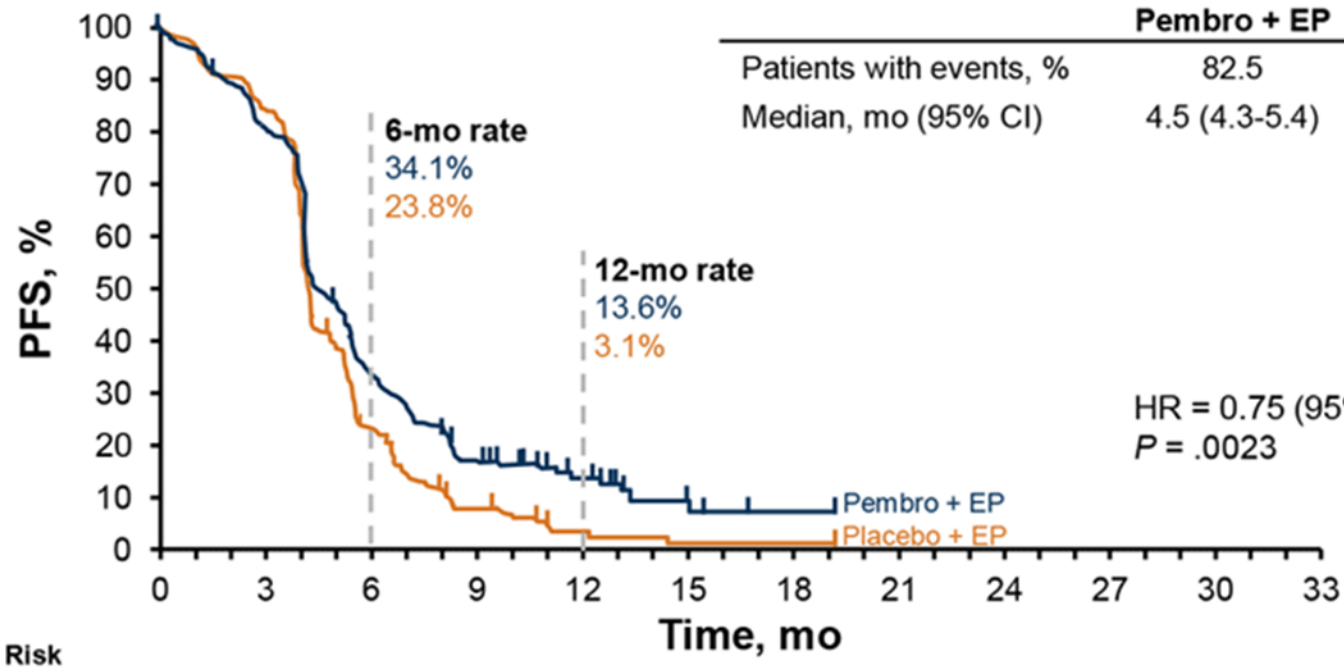


- **Dual primary endpoints:** PFS per RECIST v1.1 by BICR and OS
- **Secondary endpoints:** ORR and DOR per RECIST v1.1 by BICR and safety

[a] All brain-targeted treatment completed ≥14 d before starting study, no new or enlarging brain lesions, and neurologically stable without steroids for ≥7 d before starting study. [b] Participants with CR or PR after cycle 4 could receive up to 25 Gy of PCI in 10 fractions at investigator's discretion; PCI was to begin within 2-4 wk and no later than 6 wk after last dose of cycle 4; study treatment could continue during PCI.

1. Rudin CM et al. ASCO 2020. Abstract 9001.

KEYNOTE-604: PFS, ITT (IA2)[1]



	Pembro + EP	Placebo + EP
Patients with events, %	82.5	92.4
Median, mo (95% CI)	4.5 (4.3-5.4)	4.3 (4.2-4.4)

HR = 0.75 (95% CI, 0.61-0.91)
P = .0023

No. at Risk

Pembro + EP	228	181	71	31	15	5	1	0
Placebo + EP	225	187	50	14	3	1	1	0

Superiority threshold: one-sided *P* = .0048
Data cutoff date: March 29, 2019

Superiority threshold: one-sided *P* = .0048. Data cutoff date: March 29, 2019.

1. Rudin CM et al. ASCO 2020. Abstract 9001.

KEYNOTE-604: Results Summary[1]

- Adding pembro to EP as 1L therapy for ES-SCLC significantly improved PFS (HR = 0.75; *P* = .0023; significance threshold *P* = .0048)
- The HR for OS favored pembro + EP, but the significance threshold was missed (HR = 0.80; *P* = .0164; significance threshold *P* = .0128)
- Pembro + EP provided durable responses in a subset of participants
- Pembro + EP safety profile was as expected and manageable
- Data support the benefit of pembro and the value of immunotherapy in SCLC

1. Rudin CM et al. ASCO 2020. Abstract 9001.

Phase 2 ECOG-ACRIN EA5161: Etoposide and Platinum Chemo ± Nivo as 1L Therapy for ES-SCLC[1]

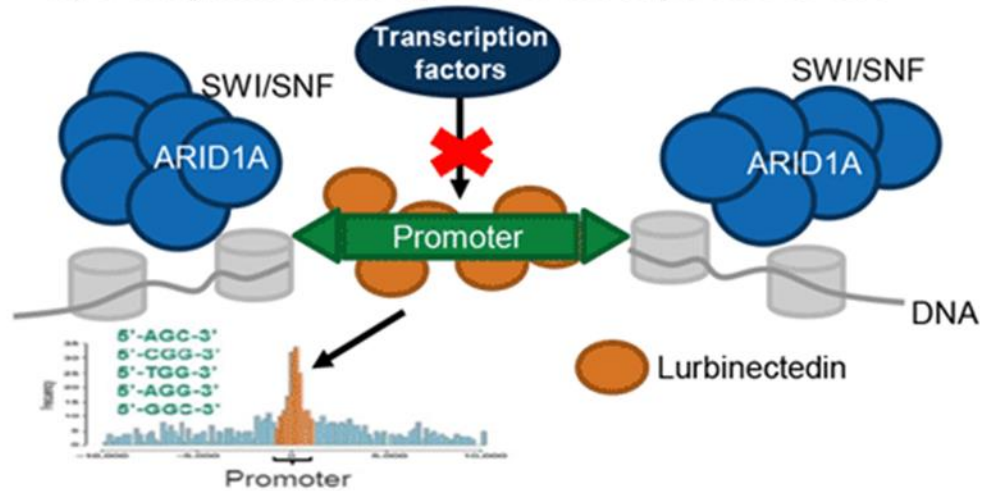
- Patients who initiated study therapy:
  - Nivolumab + chemo significantly improved PFS vs chemo, with HR = 0.68 (95% CI, 0.48-1.00; *P* = .047); mPFS 5.5 vs 4.7 mo
  - OS improved with nivolumab + chemo vs chemo, with HR = 0.73 (95% CI, 0.49-1.11; *P* = .14); mOS 11.3 vs 9.3 mo
- ITT population:
  - Nivolumab + chemo significantly improved PFS vs chemo alone, with HR = 0.65 (95% CI, 0.46-0.91; *P* = .012); mPFS 5.5 vs 4.6 mo
  - OS improved with nivolumab + chemo vs chemo, with HR = 0.67 (95% CI, 0.46-0.98; *P* = .038); mOS 11.3 vs 8.5 mo
- Combination of nivolumab + chemo was well tolerated with manageable toxicities

1. Leal TA et al. ASCO 2020. Abstract 9000.

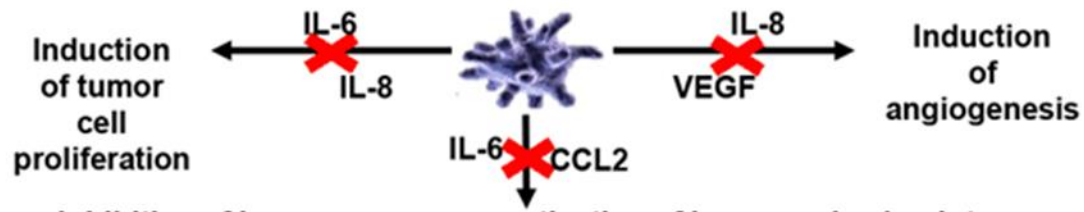
Lurbinectedin in SCLC

- Topotecan was the only FDA approved therapy for patients with platinum-sensitive SCLC in the 2L setting
- Lurbinectedin now approved for adult patients with mSCLC with disease progression on or after platinum-based chemotherapy[1]
  - Selective inhibitor of oncogenic transcription programs on which SCLC is dependent
  - Demonstrated safety and efficacy in a phase 2 basket trial[2]
  - Results awaited from phase 3 ATLANTIS trial

Cancer Is Frequently a Transcriptional Disease Caused by Deregulated Oncogenic Transcription Factors[3-5]



Inhibiting Active Transcription in TAMs , Lurbinectedin Downregulates IL-6, IL-8, CCL2, and VEGF

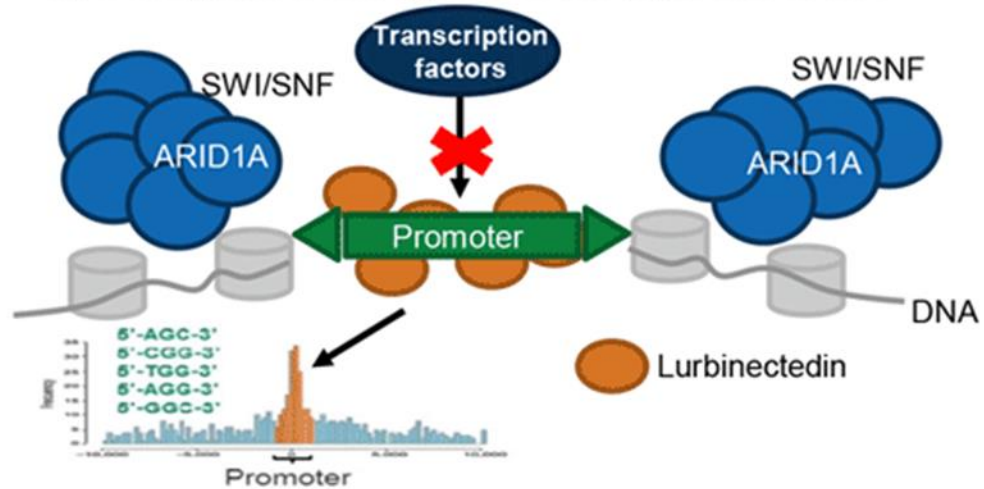


1. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-lurbinectedin-metastatic-small-cell-lung-cancer.
2. Trigo J et al. *Lancet Oncol*. 2020;21:645-654. 3. Harlow ML et al. *Cancer Res*. 2016;76:6657-6668. 4. Harlow ML et al. *Clin Cancer Res*. 2019;25:3417-3429.
5. Belgiovine C et al. *Br J Cancer*. 2017;117:628-638.

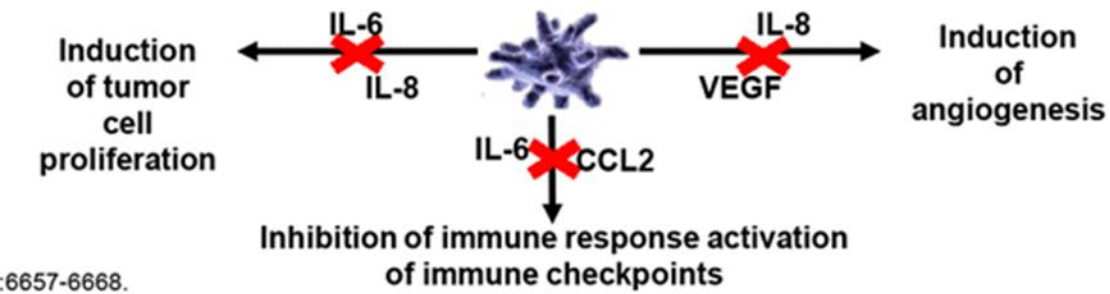
Lurbinectedin in SCLC: Mechanism of Action

- Lurbinectedin is a selective inhibitor of oncogenic transcription
  - Binds preferentially to guanines located in the GC-rich regulatory areas of DNA gene promoters
  - Prevents binding of transcription factors to their recognition sequences, inhibiting oncogenic transcription and leading to tumor cell apoptosis
  - Also affects the tumor microenvironment by inhibiting activated transcription in tumor-associated macrophages

Cancer Is Frequently a Transcriptional Disease Caused by Deregulated Oncogenic Transcription Factors[1-3]



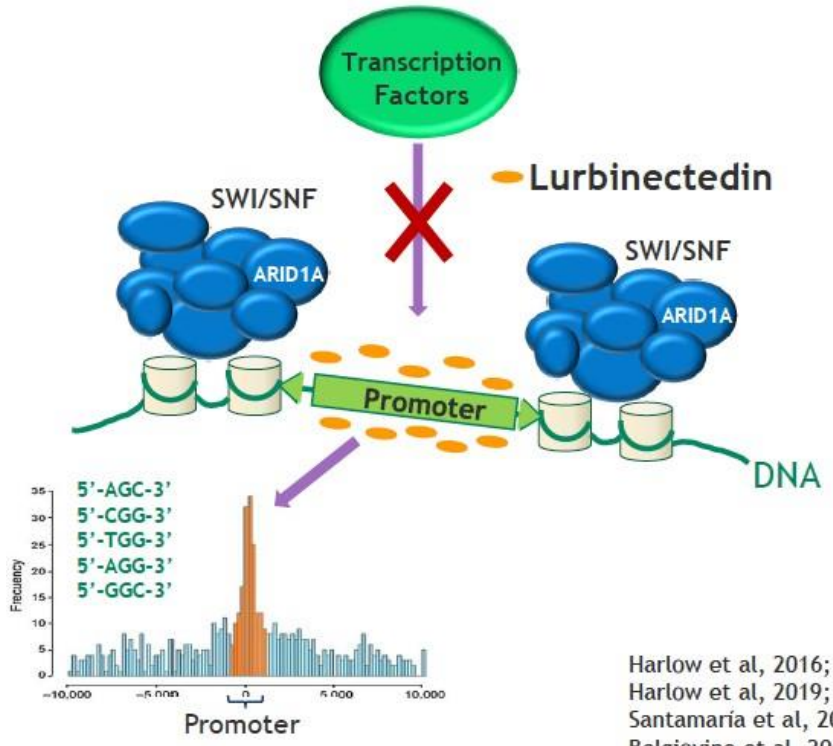
Inhibiting Active Transcription in TAMs , Lurbinectedin Downregulates IL-6, IL-8, CCL2, and VEGF



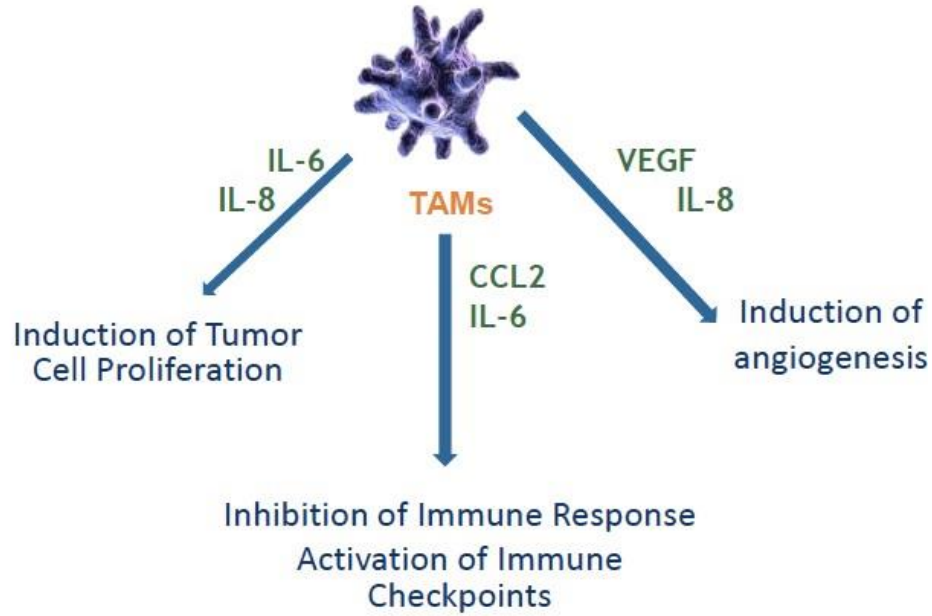
1. Trigo J et al. *Lancet Oncol*. 2020;21:645-654. 2. Harlow ML et al. *Cancer Res*. 2016;76:6657-6668.
3. Harlow ML et al. *Clin Cancer Res*. 2019;25:3417-3429.

Lurbinectedin

CANCER IS FREQUENTLY A TRANSCRIPTIONAL DISEASE CAUSED BY DEREGULATED ONCOGENIC TRANSCRIPTION FACTORS



BY INHIBITING ACTIVE TRANSCRIPTION IN TUMOR ASSOCIATED MACROPHAGES (TAMS), LURBINECTEDIN DOWNREGULATES IL-6, IL-8, CCL2 AND VEGF



Harlow et al, 2016; Cancer Res 72: 6657-68
Harlow et al, 2019; Clin Cancer Res doi: 10.1158/1078-0432.CCR-18-3511
Santamaría et al, 2016. Mol Cancer Ther 15:2399-412
Belgiovine et al, 2017 Br J Cancer 117:628-38

Paz Ares, ASCO 2019

Courtesy of David R Spigel, MD

Lurbinectidinb: Efficacy appears comparable, if not superior, to historical studies

Synthetic analog of trabectedin (selective inhibitor of oncogeniv transcription)

	Lurbinectedin (n=105)	Von Pawel 2014: Topotecan (n=213)[1]	Von Pawel 2014: Amrubicin (n=424)[1]	CheckMate 331: Chemotherapy (n=285)[2]	CheckMate 331: Nivolumab (n=284)[2]
ORR (%)	**35.2**	**16.9**	**31.1**	**16.5**	**13.7**
ORR sens (%)	45.0	23.1	40.9		
ORR res (%)	22.2	9.4	20.1		
mPFS	**3.9 m**	**3.5 m**	**4.1 m**	**3.8 m**	**1.4 m**
mPFS sens	4.6 m	4.3 m	5.5 m		
mPFS res	2.6 m	2.6 m	2.8 m		
mOS	**9.3 m** 95% CI 6.3-11.8	**7.8 m** 95% CI 6.6-8.5	**7.5 m** 95% CI 6.8-8.5	**8.4 m** 95% CI 7.0-10.0	**7.5 m** 95% CI 5.6-9.2
mOS sens	11.9 m	9.9 m	9.2 m	11.1 m	7.6 m
mOS res	5.0 m	6.2 m	5.7 m	5.7 m	7.0 m

Paz Ares L et al, ASCO 2019

1.Von Pawel et al, JCO 2014; 2 Reck et al, ESMO IO 2018

Accelerated Approval of Lurbinectedin for Metastatic SCLC

Press Release – June 15, 2020

"On June 15, 2020, the Food and Drug Administration granted accelerated approval to lurbinectedin for adult patients with metastatic small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy.

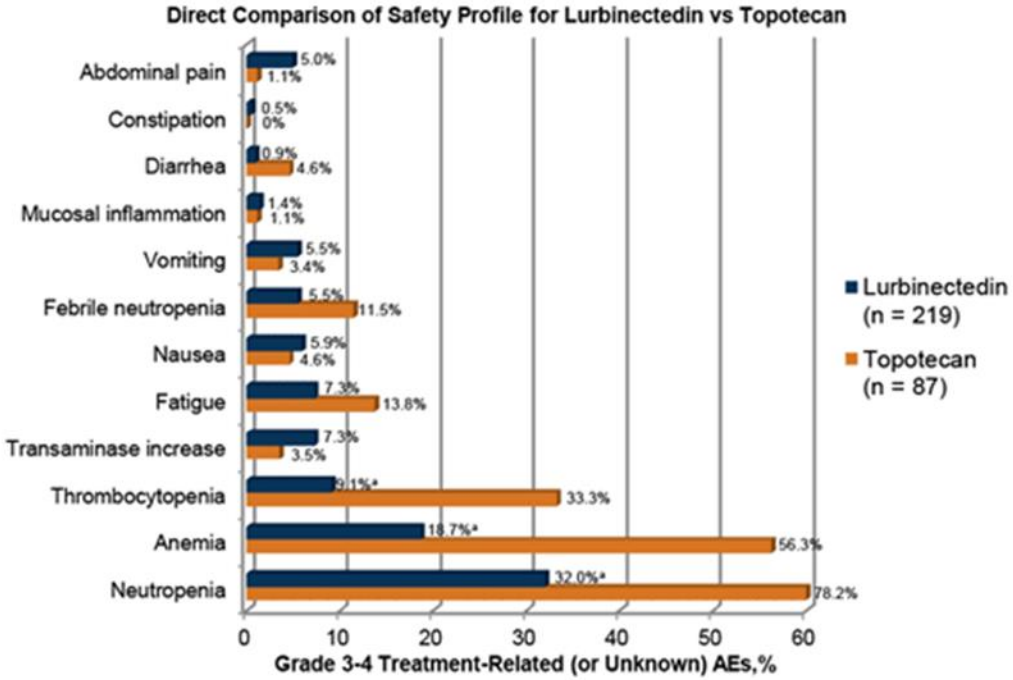
Efficacy was demonstrated in the PM1183-B-005-14 trial (Study B-005; NCT02454972), a multicenter open-label, multi-cohort study enrolling 105 patients with metastatic SCLC who had disease progression on or after platinum-based chemotherapy. Patients received lurbinectedin 3.2 mg/m^2 by intravenous infusion every 21 days until disease progression or unacceptable toxicity.

The recommended lurbinectedin dose is 3.2 mg/m^2 every 21 days."

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-lurbinectedin-metastatic-small-cell-lung-cancer.

CORAIL and Phase 2 Basket Trial Results: Pooled Safety Analysis of Single-Agent Lurbinectedin vs Topotecan[1]

- Lurbinectedin has a predictable and manageable safety profile; most common AEs were grade 1/2 fatigue, nausea, and vomiting
- TRAEs (L/T): dose reductions, 22.9%/48.3%; delays, 25.8%/52.9%; grade ≥3 SAEs, 15.0%/32.2%; discontinuations, 3.2%/5.7%, deaths, 1.3%/1.5%; G-CSF use, 23.8%/70.1%; and transfusions, 15.9%/52.9%
- Significant safety advantage observed when lurbinectedin was compared with topotecan in CORAIL in terms of hematologic toxicities; with the limitations of indirect comparisons, in the pooled safety analysis, fewer lurbinectedin-treated patients had severe hematological toxicities, SAEs, dose adjustments, treatment discontinuations, and use of supportive treatments than topotecan-treated patients



Treatment-Related (or Unknown) AE	Topotecan, % (n = 87)	Lurbinectedin, % (n = 219)
AEs of any grade	98.9	91.8
Grade ≥3	89.7	47.9
Grade ≥4	59.8	19.2
SAEs any grade	32.2	20.5
Grade ≥3 SAE	32.2	18.7
Dose delays because of AEs	52.9	25.6
Dose reductions because of AEs	48.3	16.4
Discontinuation	6.9	4.6
Deaths because of AEs	1.1	1.4
Supportive treatment		
G-CSF (secondary prophylaxis or therapeutic)[b]	70.1	24.7
RBC transfusions[b]	52.9	18.3
Platelet transfusions[b]	14.9	3.2
EPO[b]	6.9	1.8

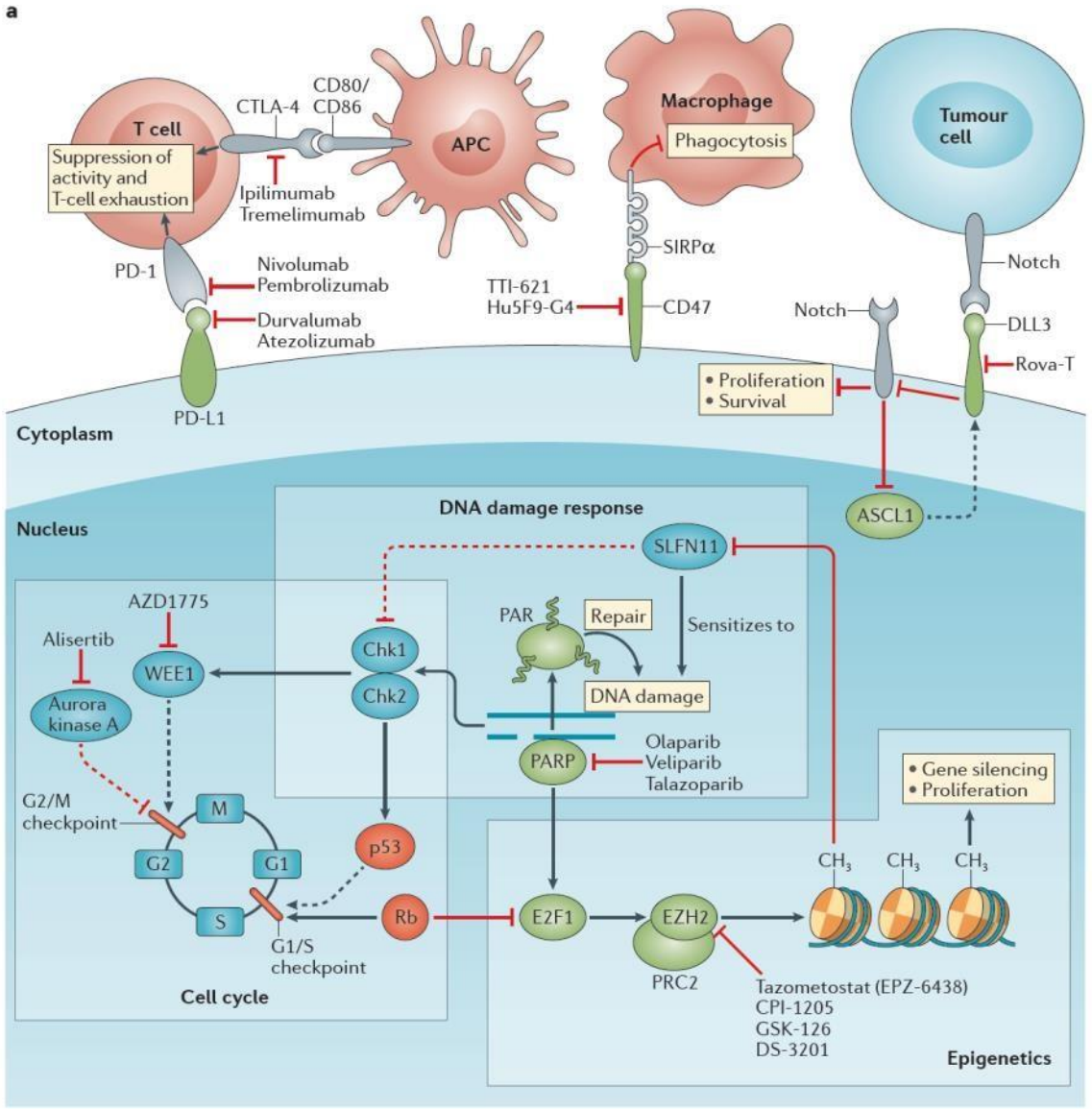
[a] Statistically significant lower incidence of severe AEs for lurbinectedin. [b] Statistical significant lower frequency of supportive treatments.

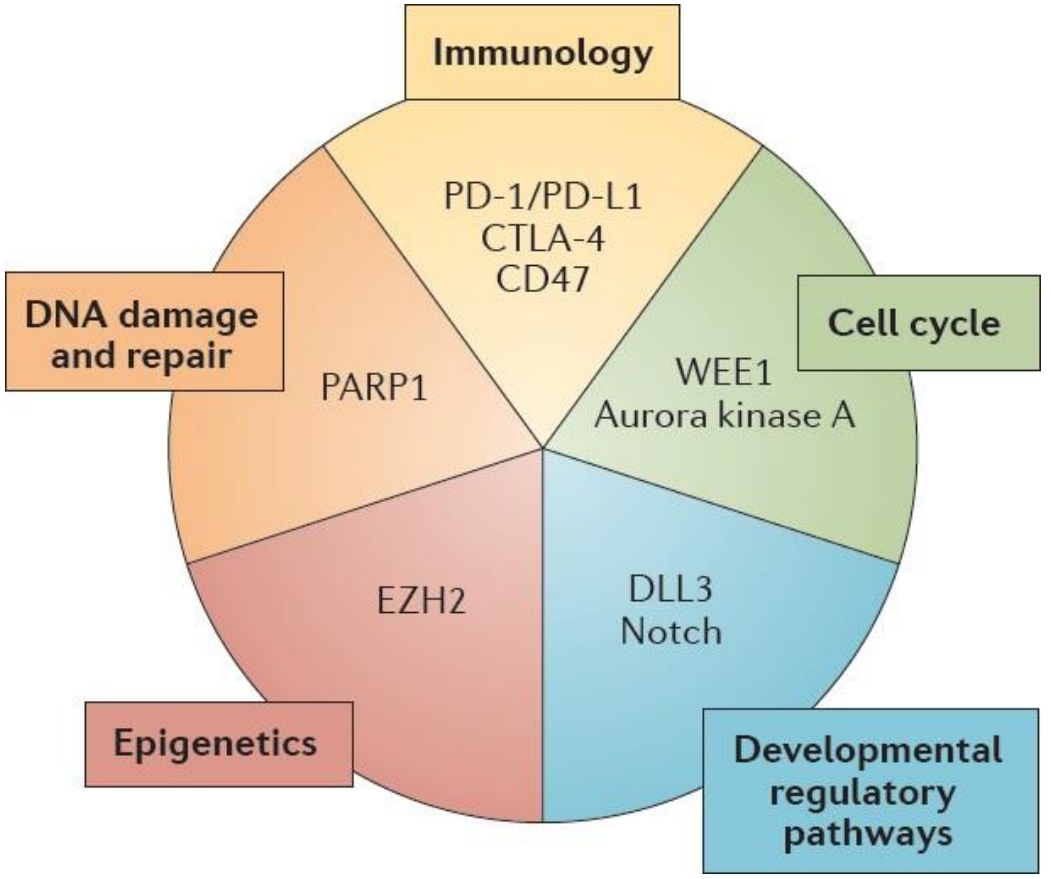
1. Leary A et al. ASCO 2020. Abstract 3635.

Where Do We Go Next With Immunotherapy and Other Novel Therapies in SCLC?

- SCLC still associated with poor outcomes and options are limited → need for more therapies
- Biomarkers needed to guide immunotherapy approaches
- New agents and combinations are under investigation

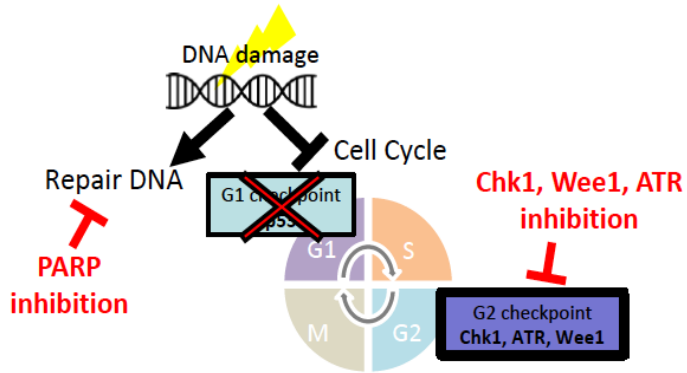
Signalling pathways focus of experimental targeted therapies for SCLC

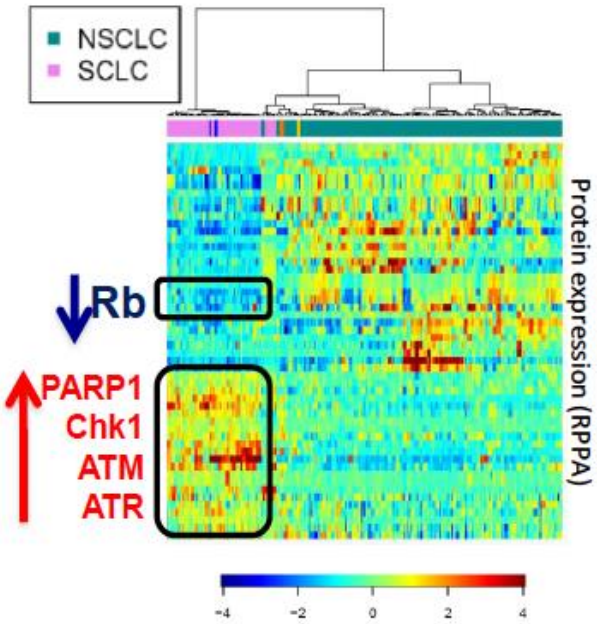




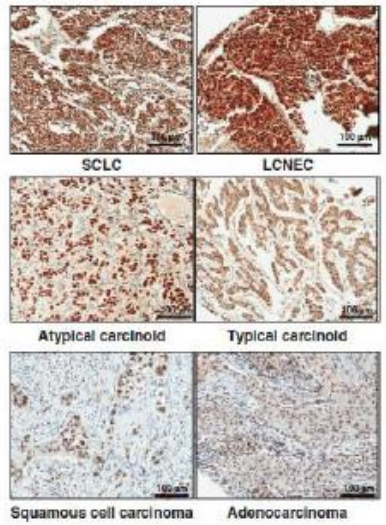
Adapted from Sabari, J. K. *et al.* (2017) Unravelling the biology of SCLC: implications for therapy *Nat. Rev. Clin. Oncol.* doi:10.1038/nrclinonc.2017.71

DNA Damage Response (DDR) proteins such as PARP1 highly expressed in SCLC

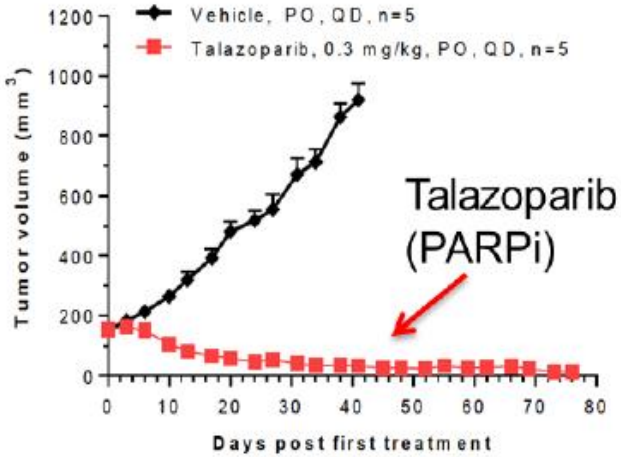




High PARP in SCLC and other NE tumors



PARP inhibition -- PDX



Byers et al. Cancer Discovery, 2012
Cardnell et al. CCR, 2013
Feng et al AACR-NCI-EORTC 2014

VOLUME 36 · NUMBER 23 · AUGUST 10, 2018
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Randomized, Double-Blind, Phase II Study of Temozolomide in Combination With Either Veliparib or Placebo in Patients With Relapsed-Sensitive or Refractory Small-Cell Lung Cancer

M. Catherine Pietanza, Saiama N. Waqar, Lee M. Krug, Afshin Dowlati, Christine L. Hann, Alberto Chiappori, Tawfeek K. Owonikoko, Kaitlin M. Woo, Robert J. Cardnell, Junya Fujimoto, Lihong Long, Licia Diao, Jing Wang, Yevgeniya Bensman, Brenda Hurtado, Patricia de Groot, Erik P. Sulman, Ignacio I. Wistuba, Alice Chen, Martin Fleisher, John V. Heymach, Mark G. Kris, Charles M. Rudin, and Lauren Averett Byers

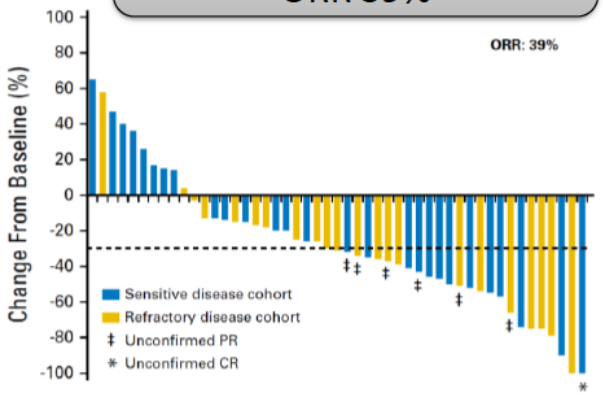
Patient population:
- 104 Recurrent SCLC, 1-2 prior regimens
- Asymptomatic brain mets allowed (21%)
- 59% platinum refractory

Dosing (28d cycle):
-Veliparib 40mg po BID x7d OR placebo
-Temozolomide 150-200mg/m² daily x5d

Clinical Outcomes

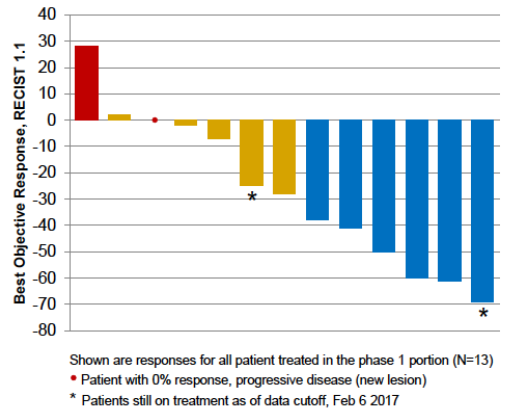
- In unselected patient population, no significant difference in 4 mo PFS, mPFS, or mOS
- ***However, ORR significantly higher in Veliparib/TMZ***
  (39% vs. 14%; p = 0.016)

Veliparib/TMZ *(n=49)*
ORR 39%



Pietanza et al, JCO 2018

Phase 1 trial of olaparib and temozolomide in SCLC (PI: Farago, NCT02446704)



Shown are responses for all patient treated in the phase 1 portion (N=13)
• Patient with 0% response, progressive disease (new lesion)
* Patients still on treatment as of data cutoff, Feb 6 2017

Objective response rate all confirmed responses **46%**

Best response	Dose level 1	Dose level 2	Dose level 3	Dose level 4	All dose levels (%)
Partial response	2	1	2	1	6 (46)
Stable disease	1	1	1	2	5 (38)
Progressive disease	0	1	1	0	2 (15)

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center Making Cancer History®

Farago et al., Presented at AACR annual meeting 2017

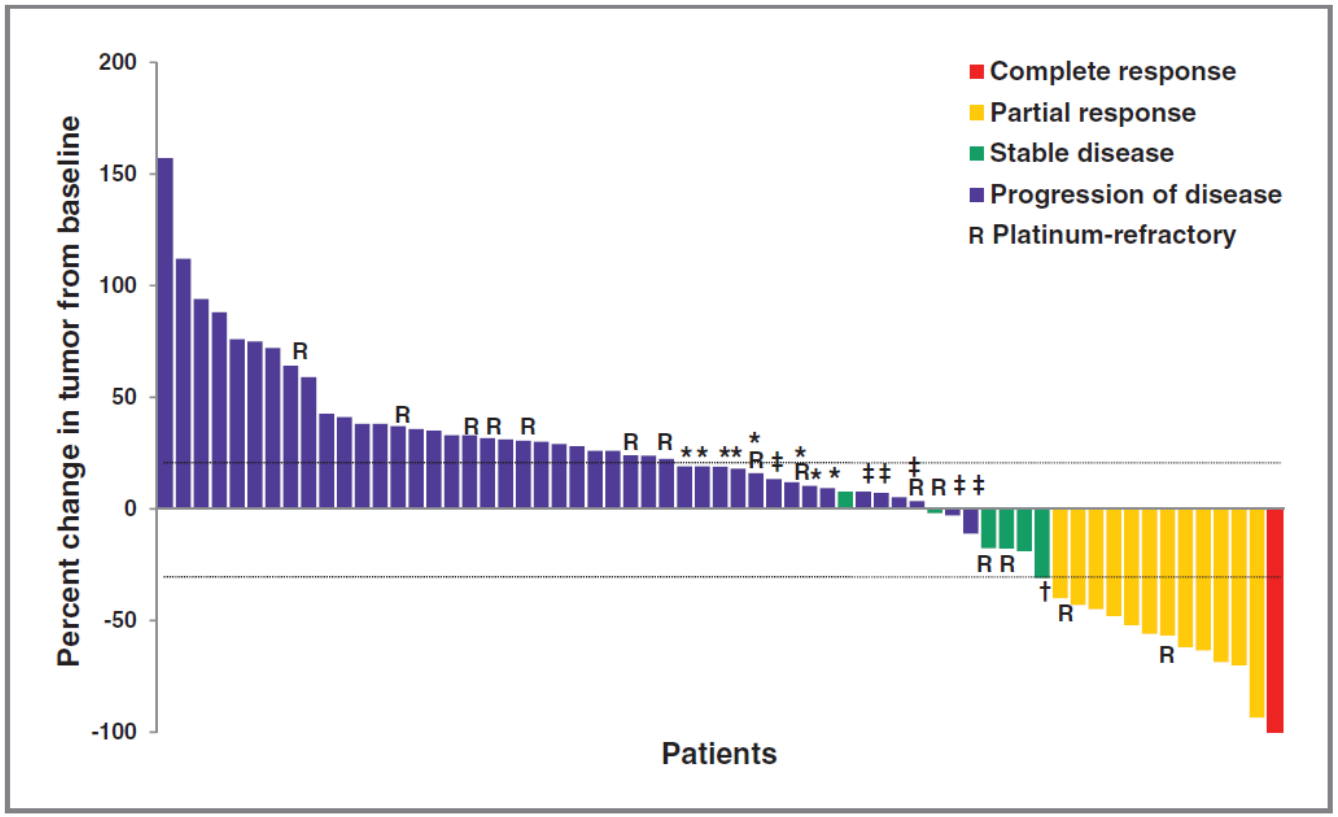
L BYERS, WCLC 2018

Cancer Therapy: Clinical

Clinical Cancer Research

Phase II Trial of Temozolomide in Patients with Relapsed Sensitive or Refractory Small Cell Lung Cancer, with Assessment of Methylguanine-DNA Methyltransferase as a Potential Biomarker

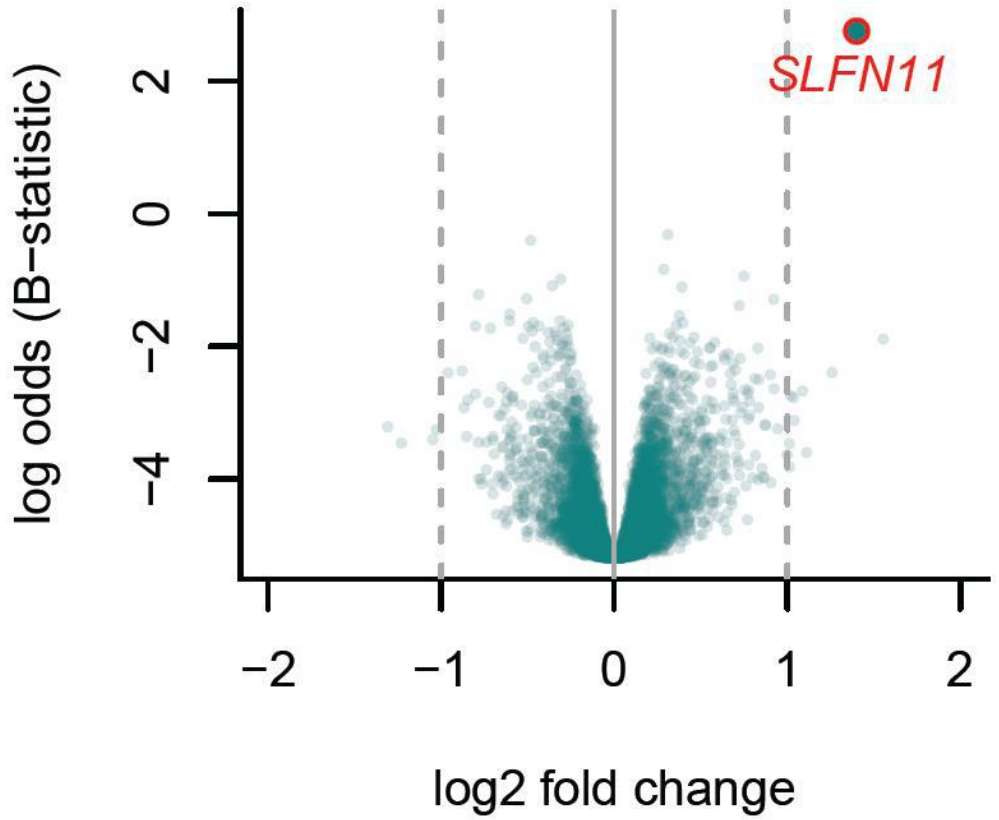
M. Catherine Pietanza[1], Kyuichi Kadota[2], Kety Huberman[3], Camelia S. Sima[4], John J. Fiore[1], Dyana K. Sumner[1], William D. Travis[2], Adriana Heguy[3], Michelle S. Ginsberg[5], Andrei I. Holodny[5], Timothy A. Chan[6], Naiyer A. Rizvi[1], Christopher G. Azzoli[1], Gregory J. Riely[1], Mark G. Kris[1], and Lee M. Krug[1]

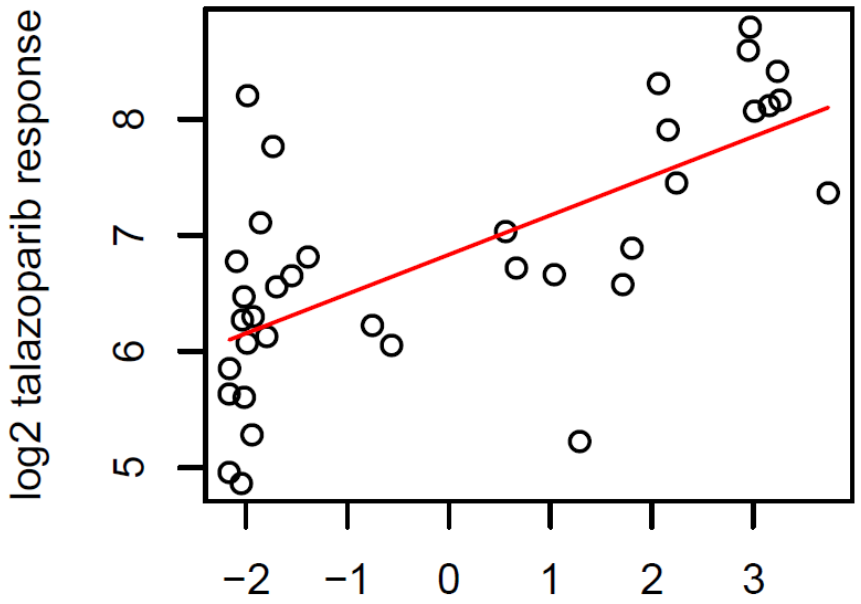


- RR 23% - platinum sensitive
- RR 13% - platinum refractory
- RR 38% - brain mets
- Thrombocytopenia, neutropenia most common side effects

Pietanza, CCR 2012

SLFN11 Predicts PARPi Sensitivity in SCLC





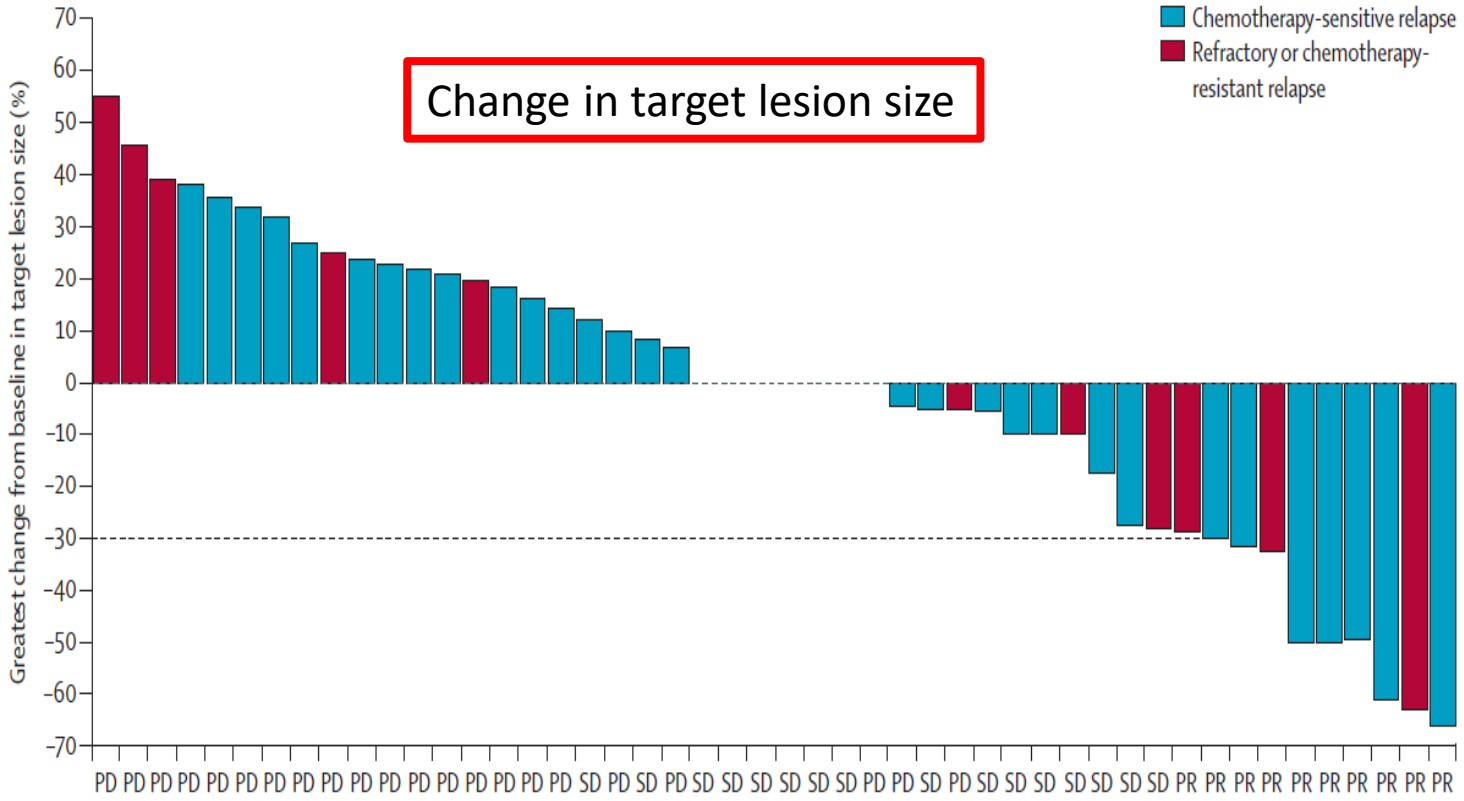
FDR $P < .008$

L BYERS, WCLC 2018

- Lok BH, et al. AACR 2016. Abstract 3756.

Aurora Kinase Inhibition

Alisertib (MLN8237) – Aurora Kinase A Inhibitor

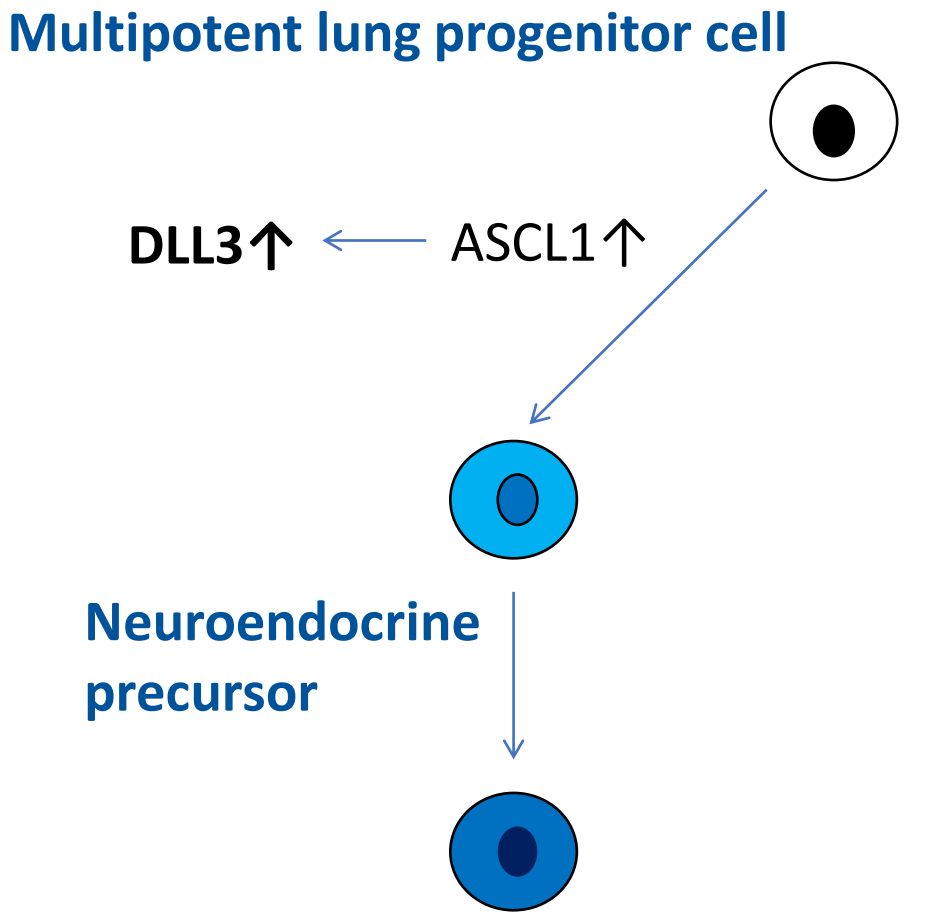


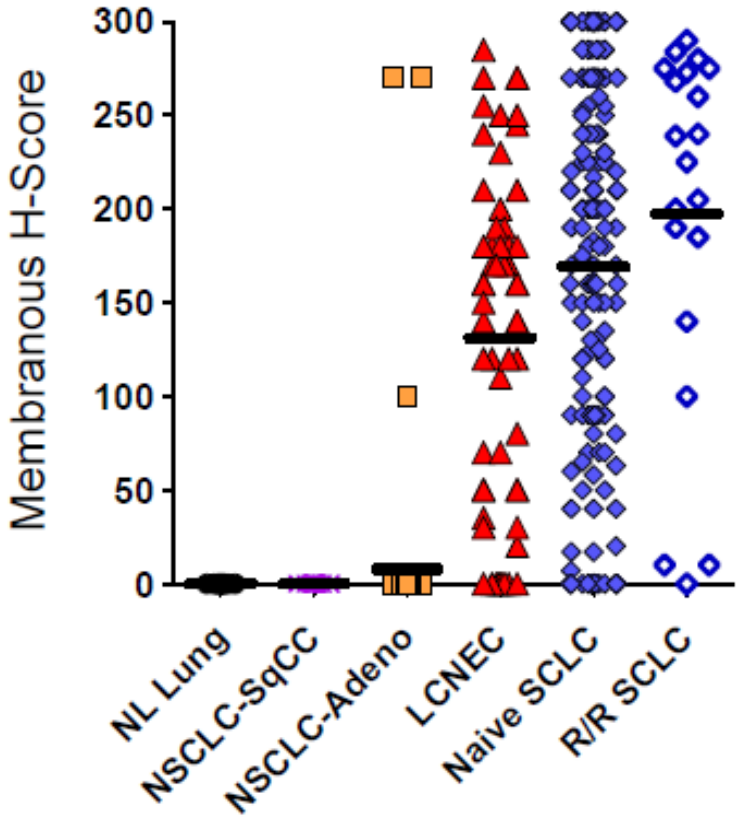
	Sensitive	Refractory/ Resistant
Patients	36	12
2nd line	47%	67%
ORR	7 (19%)	3 (25%)
DCR	20 (55%)	6 (50%)

No survival benefit

Melishar et al. *Lancet Oncol*, 2015

Harnessing neuroendocrine differentiation to target SCLC



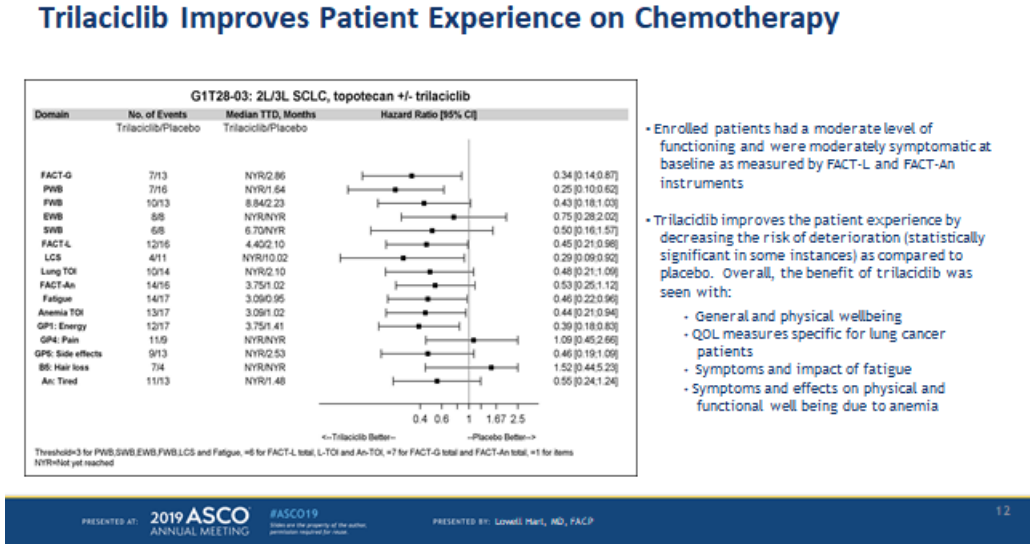


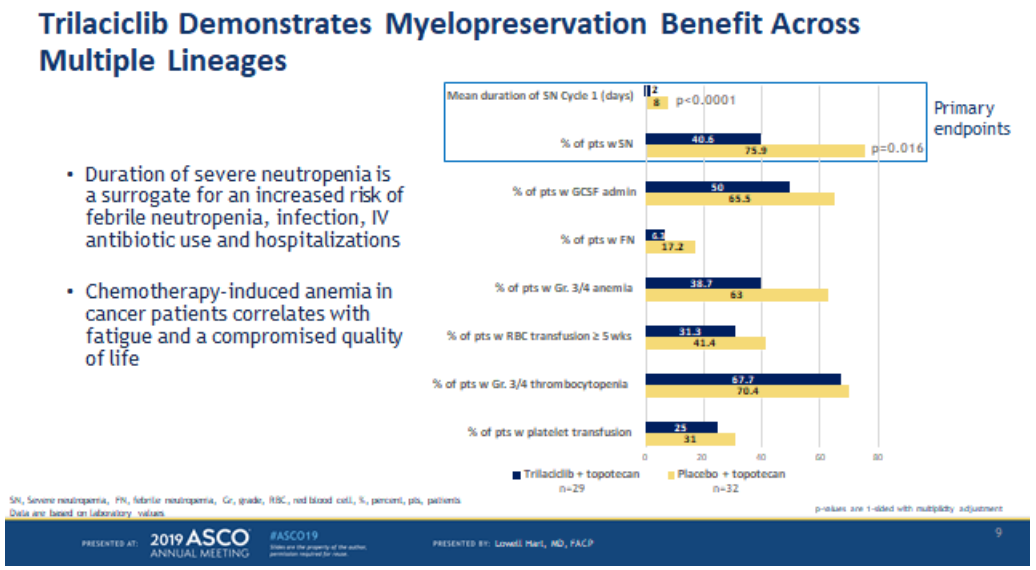
Adapted from:
Meder et al. *Int J Cancer* 2016
Linnoila et al. *Lab Invest* 2006
Saunders et al. *Sci Transl Med* 2015

FDA grants priority review to trilaciclib for small cell lung cancer

- Trilaciclib (G1 Therapeutics/Boehringer Ingelheim) is a cyclin dependent kinase 4/6 inhibitor designed to preserve bone marrow and immune system function during chemotherapy.

Trilaciclib appeared associated with reduced clinically relevant consequences of chemotherapy-induced myelosuppression, including:
67.5% reduction among patients with grade 3 or grade 4 hematologic treatment-emergent adverse events;
51.3% reduction among patients with grade 3 or grade 4 neutropenia;
83.8% reduction among patients with granulocyte colony-stimulating factors administration; and
77.5% reduction among patients with chemotherapy dose reductions.
Treatment with trilaciclib also reduced grade 3 anemia, red blood cell transfusions and grade 3 thrombocytopenia compared with placebo.
Trilaciclib appeared associated with trends toward improved ORR (66.7% vs. 62.2%), median duration of response (5.7 months vs. 4.3 months) and median PFS (6.2 months vs. 5 months; HR = 0.6; *P* = .06), but these data had not yet matured.

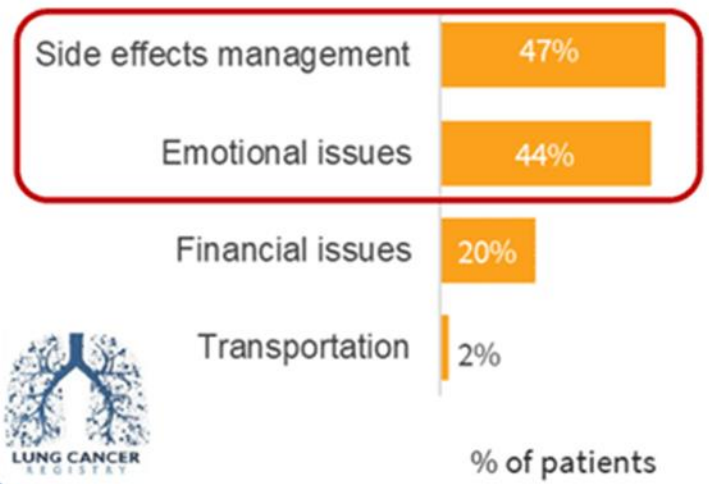




Considering the Patient Perspective

Select Findings From the GO$_2$ Lung Cancer Registry[1,2]

❑ **Areas most problematic in the past year (N = 182):**



❑ **Top five patient-reported AEs of PD-1/PD-L1 inhibitors:**

- Fatigue
- Aching joints
- Aching muscles
- Insomnia
- Itching

❑ Many patients want to participate in decisions related to their care in partnership with their clinicians, but are often not asked about their goals and concerns and have hesitations about asking questions from clinicians or expressing their opinions/preferences[3-5]

1. www.lungcancerregistry.org 2. Jim et al. 2019 American Society of Clinical Oncology Society for Immunotherapy of Cancer Clinical Immuno-Oncology Symposium (ASCO-SITC 2019); Manuscript in preparation. 3. *NQP Playbook™: Shared Decision Making in Healthcare*. 2018. 4. Alston C et al. IOM 2014. https://nam.edu/wp-content/uploads/2015/06/SDMforBestCare2.pdf. 5. Sepucha KR et al. *Med Decis Making*. 2010;30(suppl 6):775-845.

Audience Q&A