New Therapies for Squamous Cell and Small Cell Lung Carcinomas

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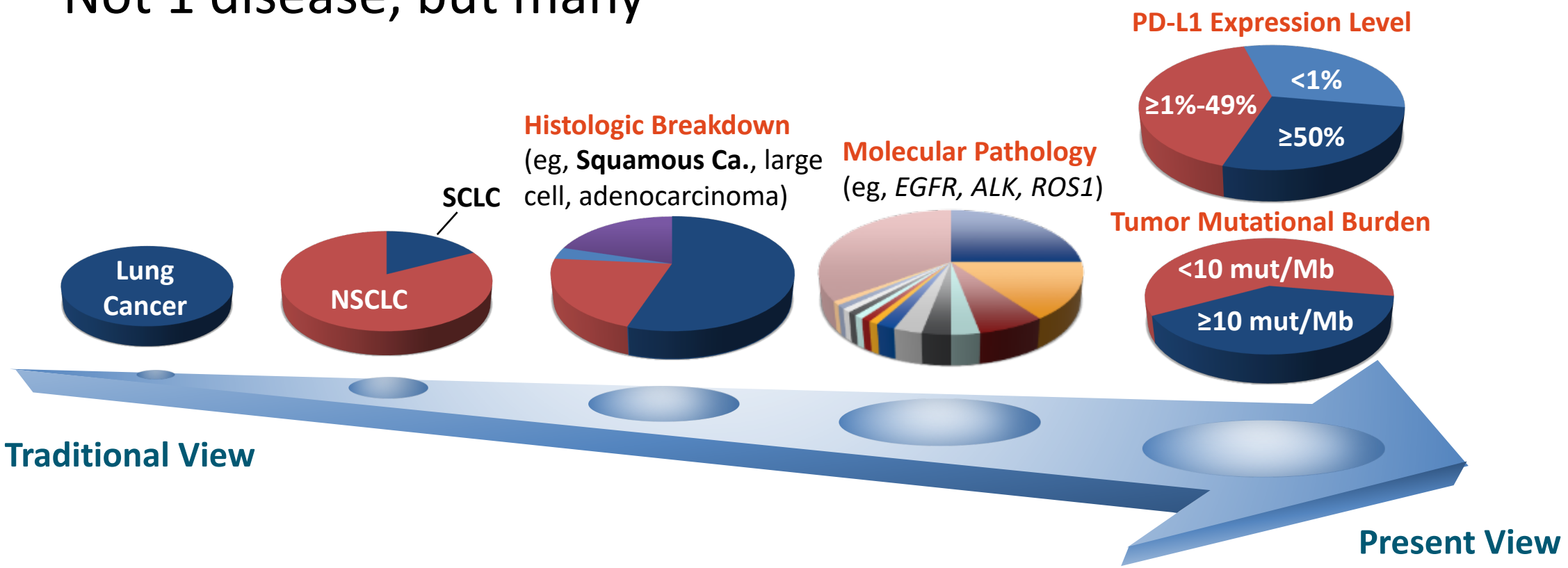
Evolution of Therapy in Lung Cancer

NSCLC – Adenocarcinoma vs. Squamous Carcinoma

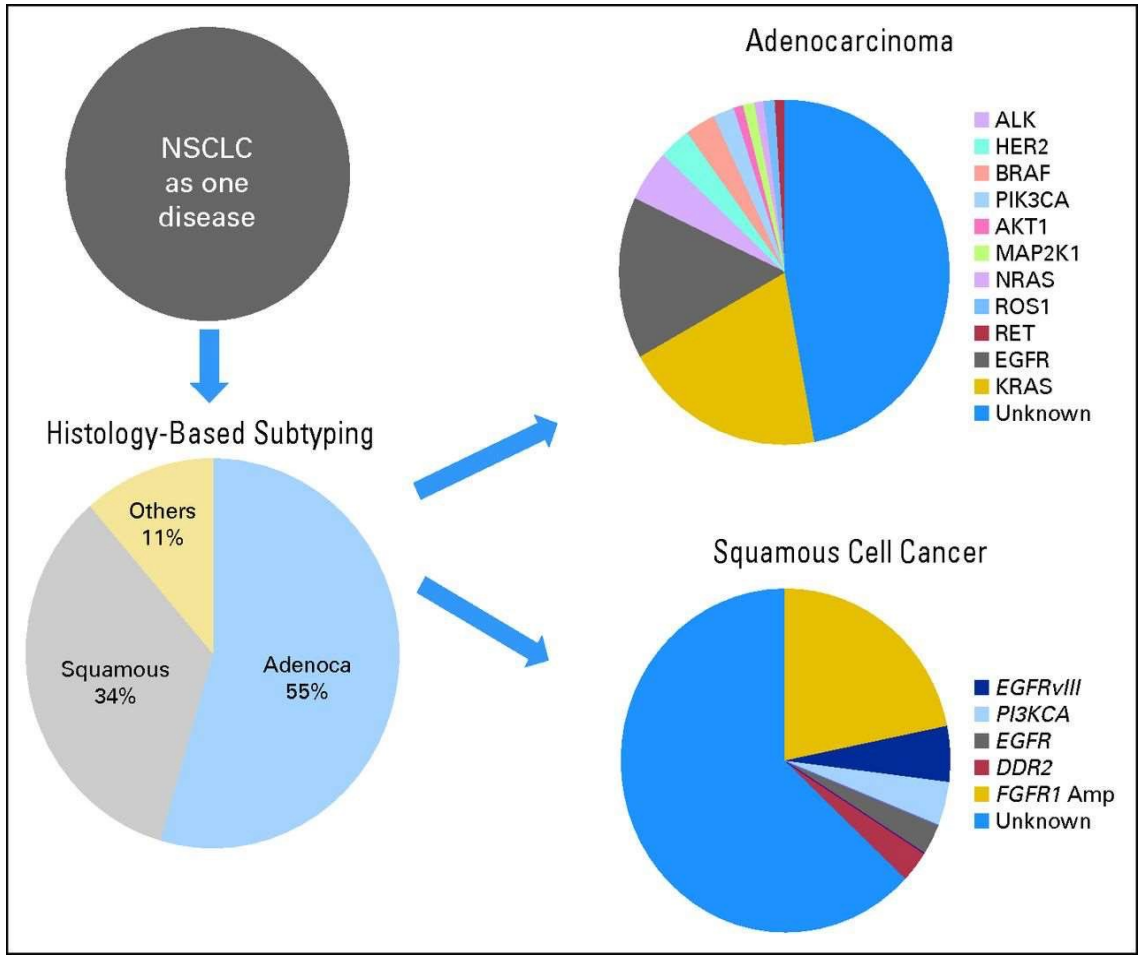
- Not 1 disease, but many



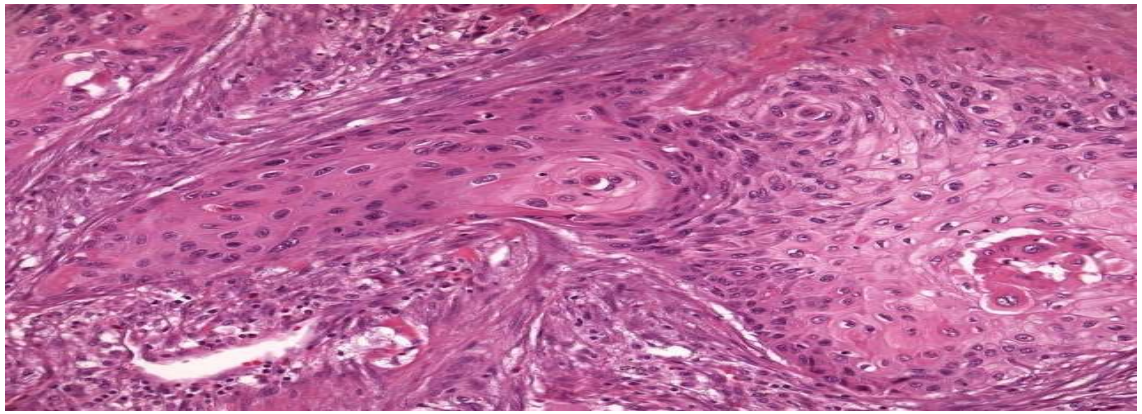
Cooper. Pathology. 2011;43:103. Langer. JCO. 2010;28:5311. Galon. Immunity. 2013;39:11.Pao. Lancet Oncol. 2011;12:175. Krigsfeld. AACR 2017. Abstr CT143. Hellmann. NEJM. 2018;378:2093.

Evolution of Therapy in Lung Cancer

Squamous Carcinoma – Molecular Targets



Li et al: J Clin Oncol 31:1039, 2013



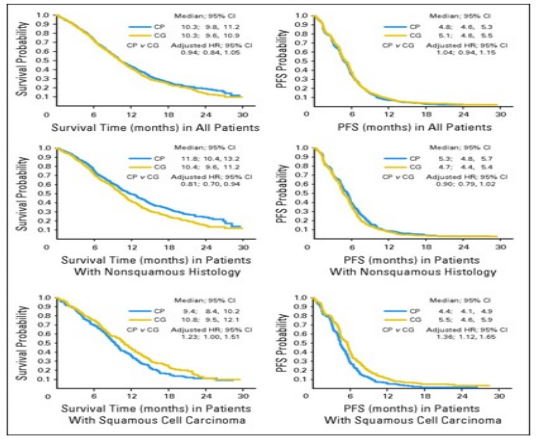
- 20-30% of NSCLC
- Strongly associated with cigarette smoking
- Historically was treated like lung adenocarcinomas
- Despite advances in the personalized treatment of adenocarcinoma, effective targeted therapy for squamous cell has remained elusive
- Squamous cell lung cancer lacks druggable targets
- Most substantial impact in treatment has come from histology agnostic approaches

Squamous Cell Carcinoma

Treatment Evolution: Chemotherapy, moAbs, TKIs

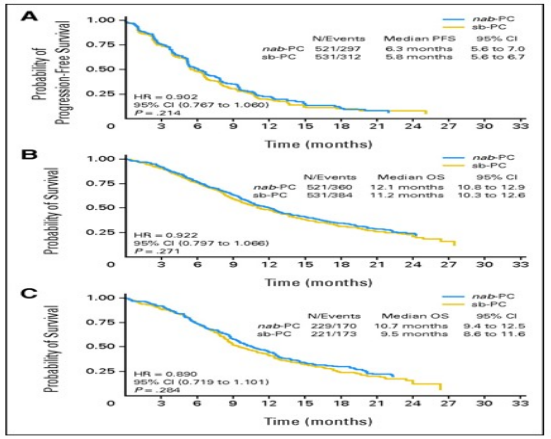
Chemotherapy: Pemetrexed and nab-Paclitaxel

Non Squamous



Giorgio Vittorio Scagliotti et al. JCO 2008;26:3543-3551

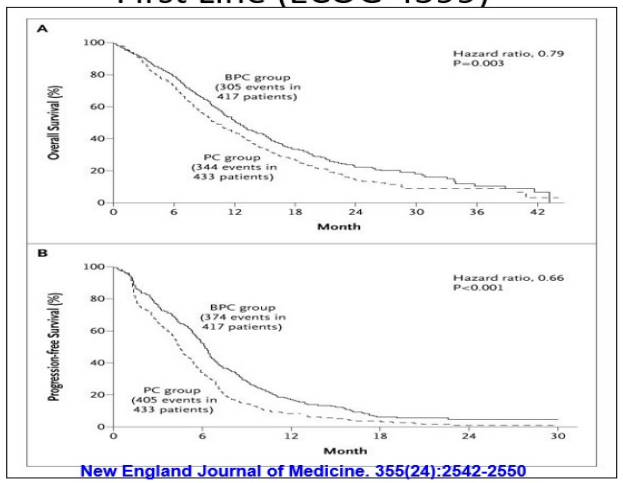
Squamous



Mark A. Socinski et al. JCO 2012;30:2055-2062

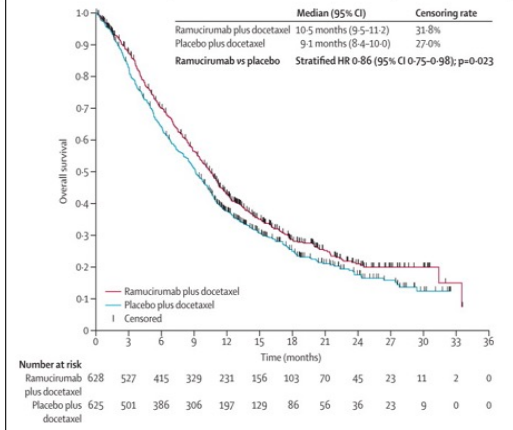
Biologics (anti-VEGFR): Bevacizumab and Ramucirumab

First Line (ECOG 4599)



New England Journal of Medicine. 355(24):2542-2550

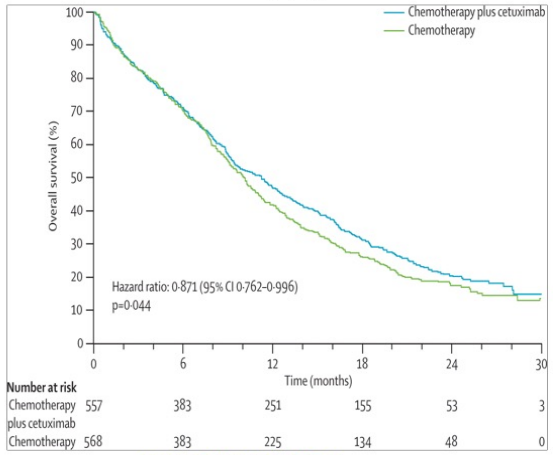
Second Line (REVEL)



Lancet 2014, 384(9944): 665–673

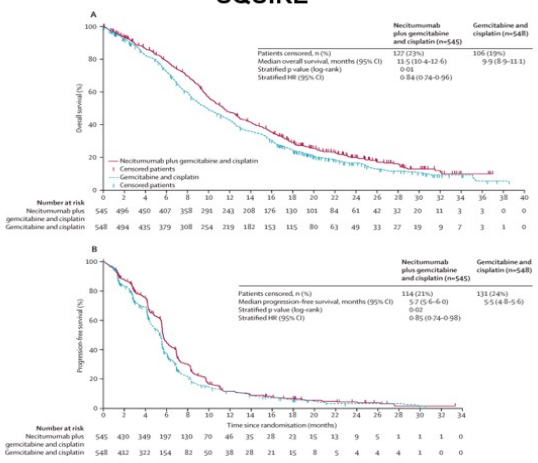
Biologics (anti-EGFR): Cetuximab and Necitumumab

FLEX



Lancet 2009; 373: 1525–31

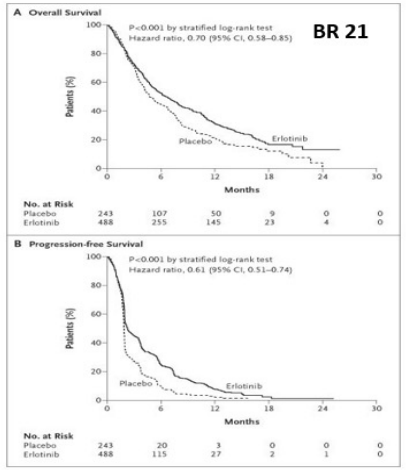
SQUIRE



Lancet Oncology 2015, 16(7): 763–774

TKI: Erlotinib and Afatinib

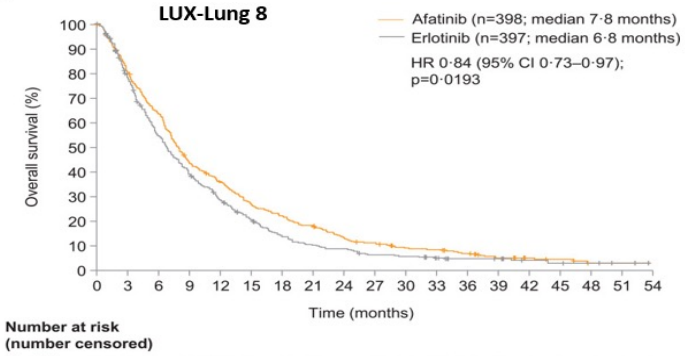
BR 21



N Engl J Med 2005 Jul 14;353(2):123-32

A

LUX-Lung 8



Number at risk (number censored)

Afatinib 398 317 250 170 138 103 85 68 49 40 31 29 22 13 8 6 2 2 0
(0) (4) (5) (6) (8) (8) (8) (8) (10) (11) (13) (13) (15) (19) (24) (25) (27) (27) (29)

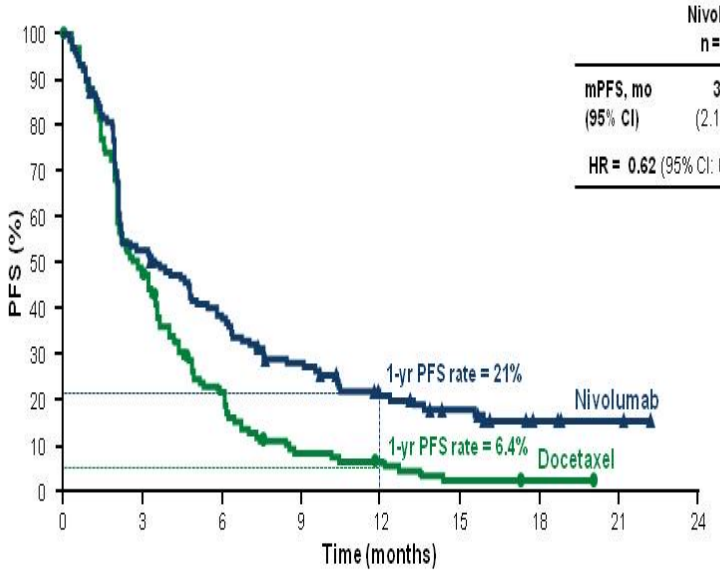
Erlotinib 397 305 210 150 108 75 51 37 32 22 19 15 11 10 5 3 2 0 0
(0) (7) (10) (10) (12) (14) (15) (15) (16) (16) (18) (21) (22) (26) (27) (28) (30) (30)

EClinicalMedicine. 2021 Jul; 37: 100940.

Nivolumab

Phase III Squamous NSCLC – CM-017

Progression-Free Survival



	Nivolumab n = 135	Docetaxel n = 137
mPFS, mo (95% CI)	3.5 (2.1, 4.9)	2.8 (2.1, 3.5)

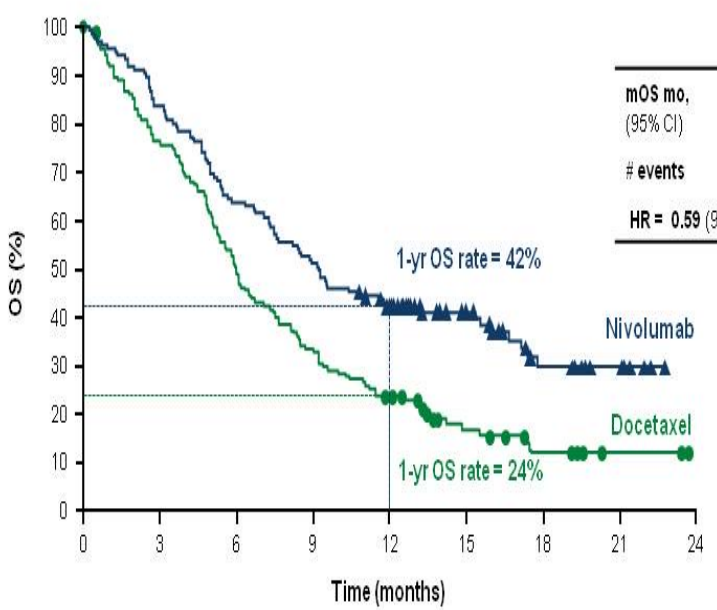
HR = 0.62 (95% CI: 0.47, 0.81); *P* = 0.0004

Number of Patients at Risk									
Nivolumab	135	68	48	33	21	15	6	2	0
Docetaxel	137	62	26	9	6	2	1	0	0

PFS per investigator.

PRESENTED AT: ASCO Annual '15 Meeting

Overall Survival



	Nivolumab n = 135	Docetaxel n = 137
mOS mo, (95% CI)	9.2 (7.3, 13.3)	6.0 (5.1, 7.3)
# events	86	113

HR = 0.59 (95% CI: 0.44, 0.79), *P* = 0.00025

Number of Patients at Risk									
Nivolumab	135	113	86	69	52	31	15	7	0
Docetaxel	137	103	68	45	30	14	7	2	0

Symbols represent censored observations

PRESENTED AT: ASCO Annual '15 Meeting

Presented By David Spigel at 2015 ASCO Annual Meeting

Single-Agent ICI for Advanced NSCLC

High PD-L1 Expression

KEYNOTE-024

- Open-label, randomized phase III study

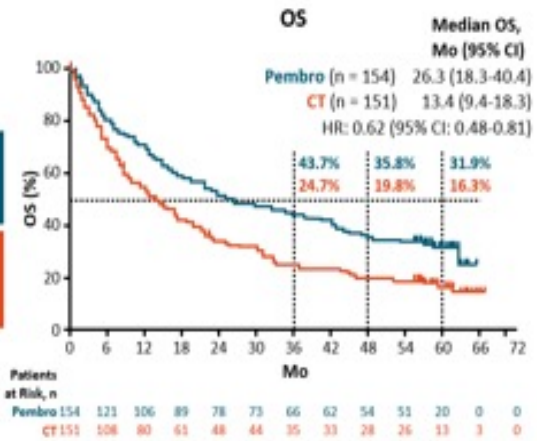
Stratified by ECOG PS (0 vs 1), histology (squamous vs nonsquamous), and enrollment site

Chemotherapy-naive, stage IV NSCLC; PD-L1 selected (TPS ≥50%*); ECOG PS 0/1; no *EGFR/ALK* mutations; no untreated CNS mets or autoimmune disease requiring tx (N = 305)

- **Pembrolizumab** 200 mg IV Q3W for up to 35 cycles (n = 154)
- **Platinum-Doublet CT** (histology based) for 4-6 cycles (n = 151)

*Staining of ≥50% tumor cells by 22C3 companion diagnostic IHC assay.

Reck. JCO. 2021;21:2339.



IMpower110

- Randomized phase III study

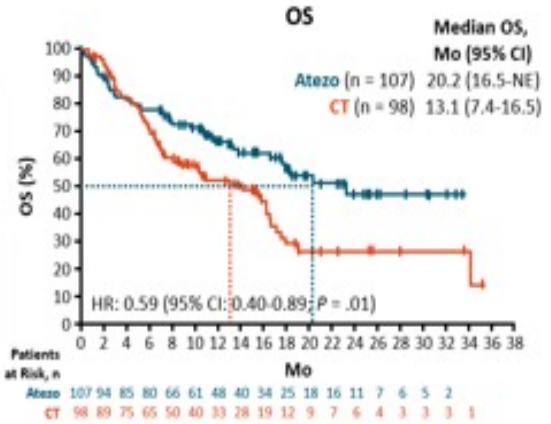
Stratified by sex, ECOG PS, histology, and tumor PD-L1 status

Untreated LA or metastatic NSCLC of any histology; PD-L1 ≥50% on TC or 10% on IC*; no sensitizing *EGFR* or *ALK* alterations; ECOG PS 0/1; no untreated or unstable CNS mets or pneumonitis requiring tx (N = 205†)

- **Atezolizumab** 1200 mg Q3W until PD (n = 107)
- **Platinum-Doublet CT** (histology based) for 4-6 cycles (n = 98)

*Staining of ≥50% tumor cells (TC3) or ≥10% tumor-infiltrating immune cells (IC3) using SP142 complementary diagnostic IHC assay.
†572 patients with PD-L1 ≥1% on TC or IC enrolled overall.

Herbst. NEJM. 2020;383:1328.



EMPOWER-Lung 1

- Randomized phase III study

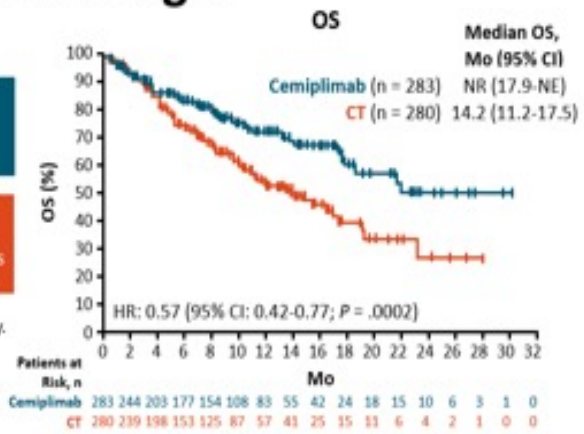
Stratified by histology (squamous vs nonsquamous) and region (Europe, Asia, vs ROW)

Treatment naive advanced NSCLC, PD-L1 ≥50%*; no *EGFR/ALK/ROS1* mutations, ECOG PS 0/1 (N = 563†)

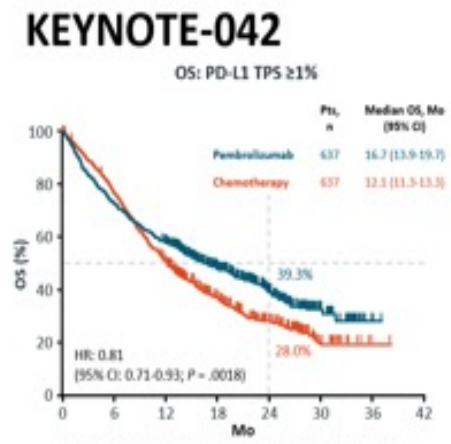
- **Cemiplimab** 350 mg Q3W Until PD or 108 wk
- **Platinum-Doublet CT** (histology based) for 4-6 cycles

*Staining of ≥50% tumor cells using 22C3 companion diagnostic IHC assay.
†710 patients enrolled in overall ITT population.

Sezer. Lancet. 2021;397:592.

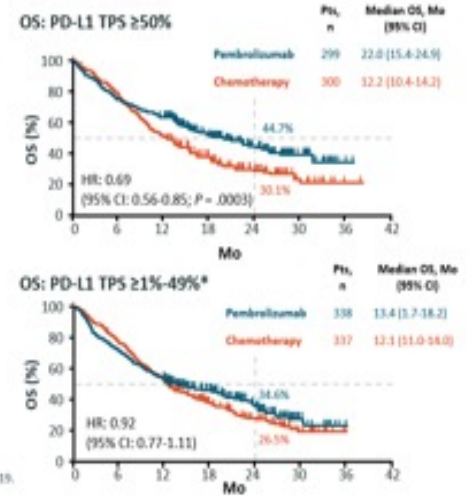


KEYNOTE-042



*Exploratory analysis; no alpha allocated to this comparison.

Mok. Lancet. 2019;393:1819.



Chemo-IO Combinations for Advanced NSCLC

Histology based

Trial	Comparison	Selection	ORR, %	PFS HR	OS HR
KEYNOTE-189[1,2]	Pembro or placebo + carbo/pem	PD-L1 unselected; nonsq	48.3 vs 19.9	0.49	0.56
IMpower130[3]	Atezo + carbo/nab-pac vs CT alone	PD-L1 unselected; nonsq	49.2 vs 31.9	0.64	0.79
IMpower150[4,5]	Atezo + carbo/pac + bev vs CT + bev	PD-L1 unselected; nonsq*	63.5 vs 48.0	0.62	0.80
KEYNOTE-407[6-8]	Pembro or placebo + carbo/pac or nab-pac	PD-L1 unselected; sq	62.6 vs 38.8	0.59	0.71
IMpower131[9]	Atezo + carbo/nab-pac vs CT alone	PD-L1 unselected; sq		0.71	0.96

*WT population (excludes patients with *EGFR* or *ALK* alterations).

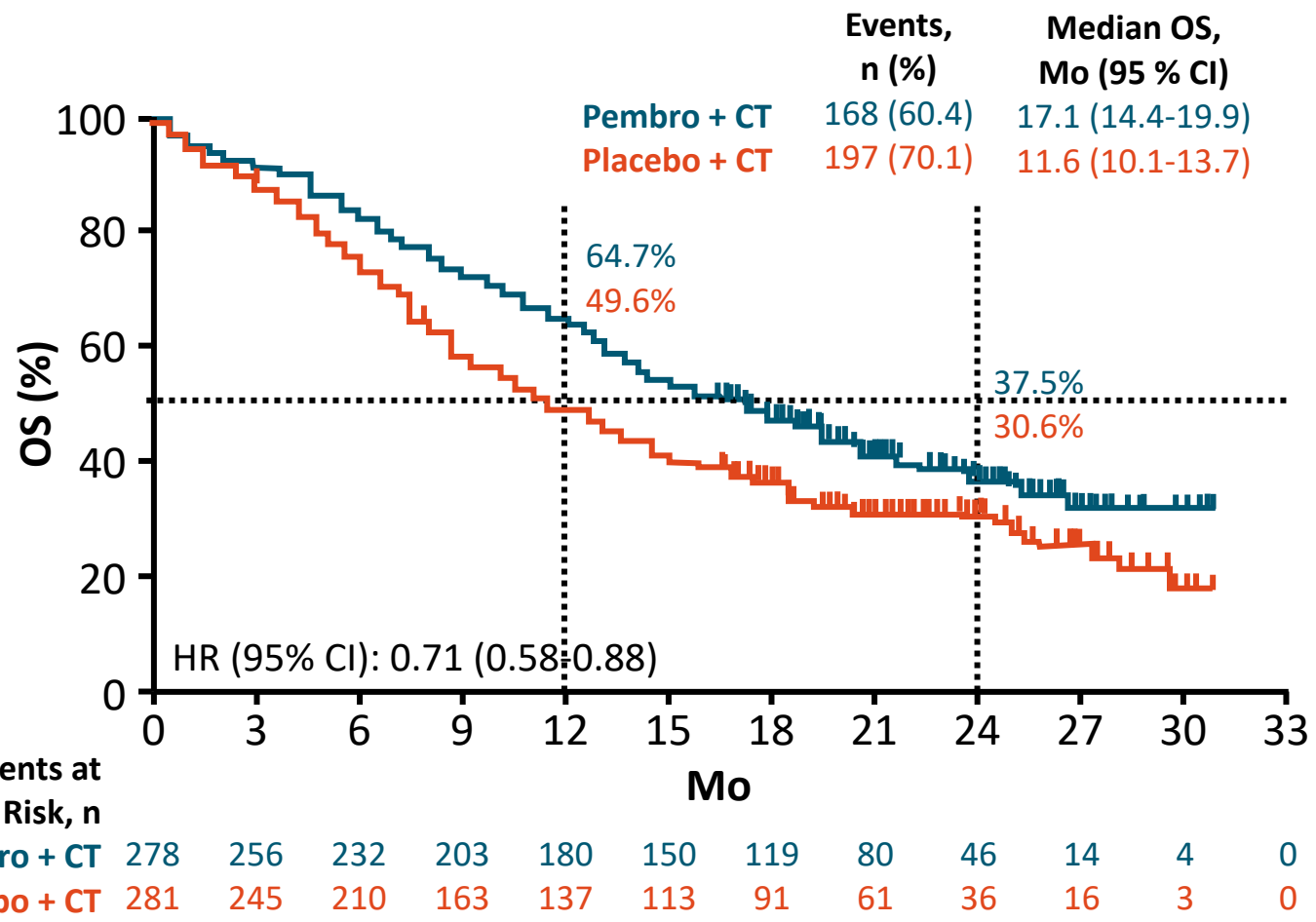
- FDA approvals
  - No *EGFR* or *ALK* alterations
  - PD-L1 agnostic; OS benefit observed in all subgroups

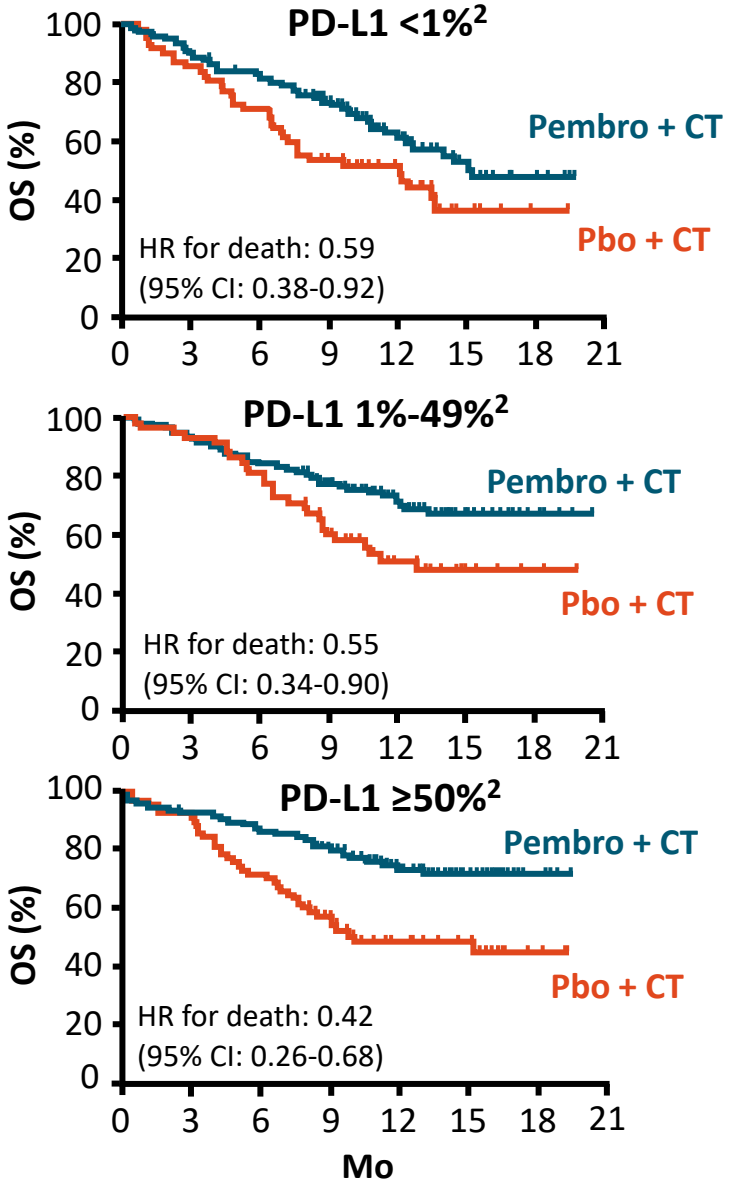
1. Gandhi. NEJM. 2018;378:2078. 2. Rodríguez-Abreu. Ann Oncol. 2021;32:881. 3. West. Lancet Oncol. 2019;20:924. 4. Socinski. NEJM. 2018;378:2288. 5. Sociniski. AACR 2020. Abstr CT216. 6. Paz-Ares. NEJM. 2018;379:2040. 7. Paz-Ares. J Thorac Oncol. 2020;15:1657. 8. Robinson. ELCC 2021. Abstr 97O.
9. Presented By Robert Jotte at 2018 ASCO Annual Meeting

KEYNOTE-407:

Pembrolizumab + Chemotherapy

OS in ITT Population[1]

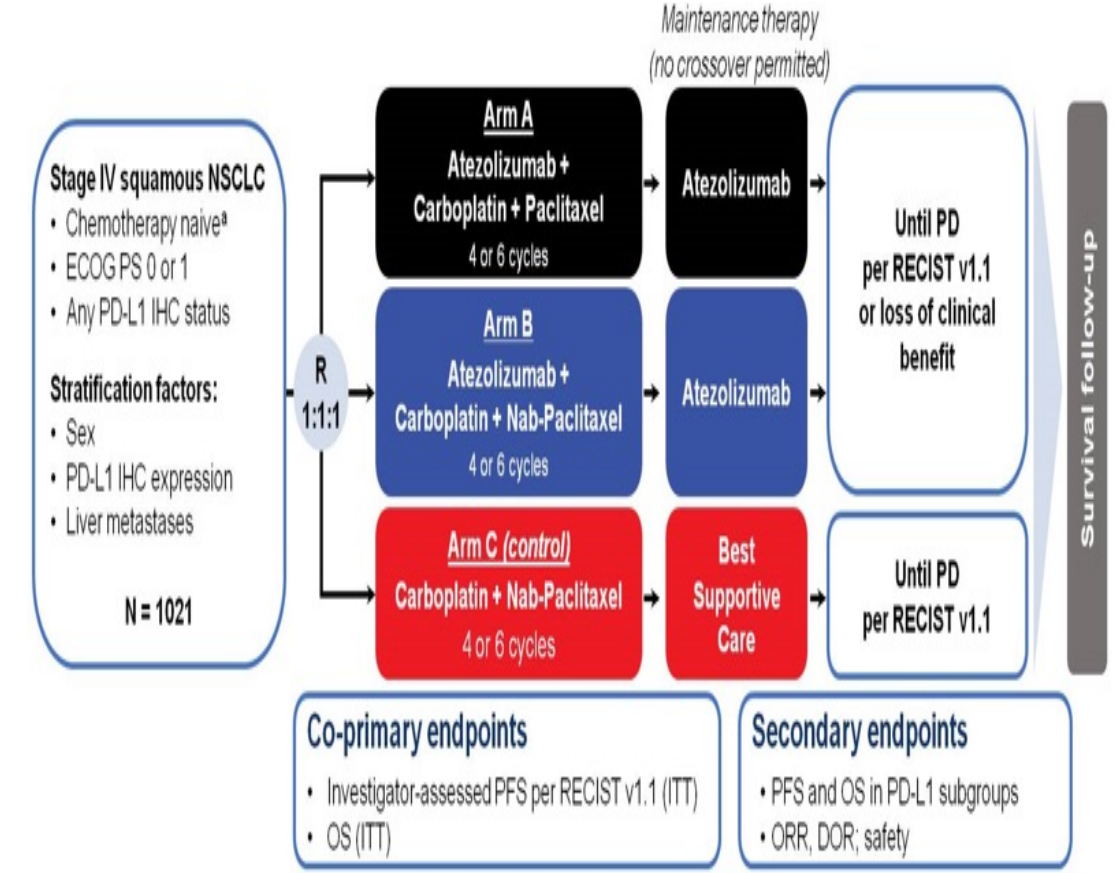




1. Paz-Ares. J Thorac Oncol. 2020;15:1657. 2. Gandhi. NEJM. 2018;378:2078.

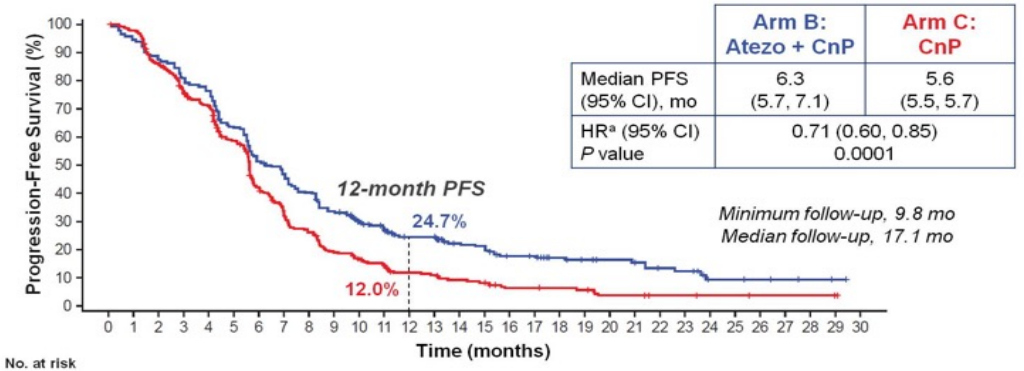
IMpower 131

Atezolizumab + Chemotherapy



Atezolizumab 1200 mg IV q3w; carboplatin AUC 6 IV q3w; nab-paclitaxel 100 mg/m^2 IV qw; paclitaxel 200 mg/m^2 IV q3w.
[a] Patients with a sensitising *EGFR* mutation or *ALK* translocation must have disease progression or intolerance to treatment with ≥ 1 approved targeted therapies. Testing for *EGFR* mutation or *ALK* translocation was not mandatory.
[b] PD-L1 expression was evaluated using the VENTANA SP142 IHC assay.

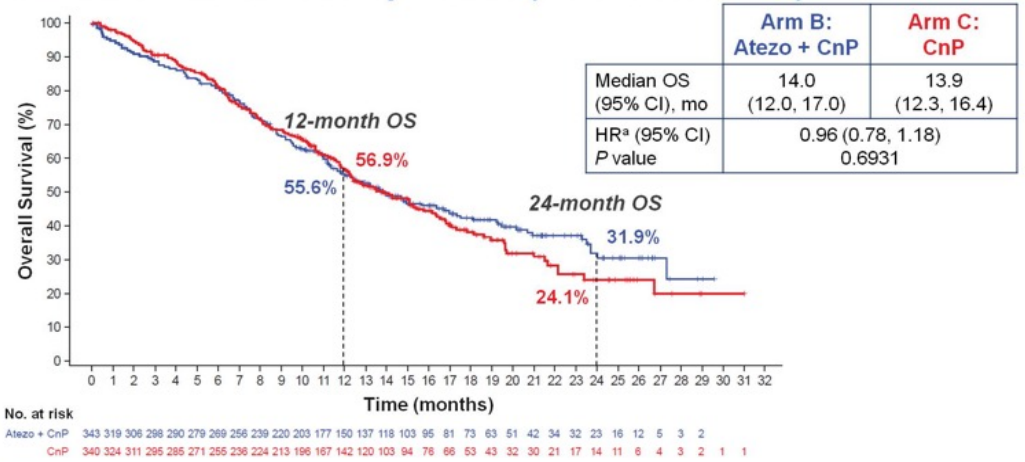
INV-Assessed PFS in the ITT Population (Arm B vs Arm C)



	Arm B: Atezo + CnP	Arm C: CnP
Median PFS (95% CI), mo	6.3 (5.7, 7.1)	5.6 (5.5, 5.7)
HR[a] (95% CI) *P* value	0.71 (0.60, 0.85) 0.0001	

Data cutoff: January 22, 2018.
INV, investigator. [a] Stratified HR.

First Interim OS in the ITT Population (Arm B vs Arm C)



	Arm B: Atezo + CnP	Arm C: CnP
Median OS (95% CI), mo	14.0 (12.0, 17.0)	13.9 (12.3, 16.4)
HR[a] (95% CI) *P* value	0.96 (0.78, 1.18) 0.6931	

Data cutoff: January 22, 2018.
[a] Stratified HR.

ICI Combinations

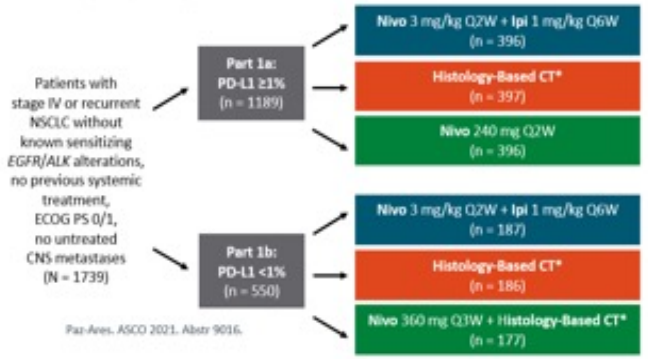
With and without Chemotherapy

CheckMate 227

First-line Nivolumab + Ipilimumab vs Chemotherapy

- Randomized, open-label, multipart phase III trial

Stratified by histology (squamous vs nonsquamous)



Paz-Ares. ASCO 2021. Abstr 9016.

Up to 2 yr for immunotherapy

- **Dual primary endpoints for nivo + ipi vs CT**
  - PFS in high TMB (≥10 mut/Mb) population
  - OS in PD-L1 ≥1% population

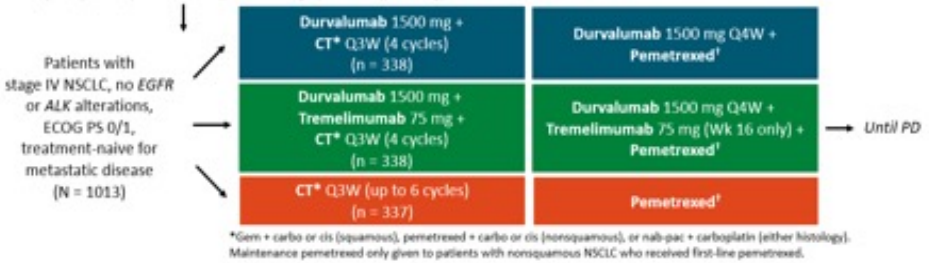
**Nonsquamous:* pemetrexed + cisplatin or carboplatin Q3W for ≤4 cycles with optional maintenance (pemetrexed after CT, or nivo + pemetrexed after nivo + pemetrexed)
***Squamous:* gemcitabine + cisplatin or carboplatin Q3W for ≤4 cycles.**

POSEIDON

First-line Durvalumab ± Tremelimumab + Chemotherapy in NSCLC

- Open-label, multicenter, randomized phase III trial

Stratified by PD-L1 (≥50% vs <50%), disease stage (IVA vs IVB), histology



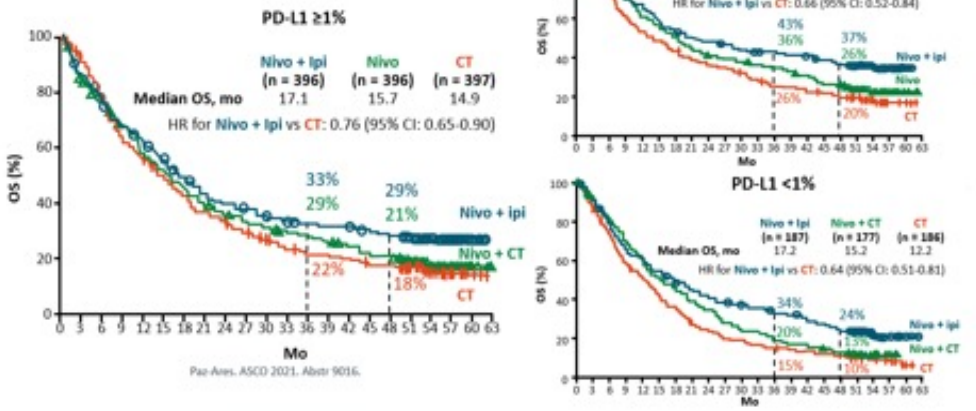
*Gem + carbo or cis (squamous), pemetrexed + carbo or cis (nonsquamous), or nab-pac + carboplatin (either histology). Maintenance pemetrexed only given to patients with nonsquamous NSCLC who received first-line pemetrexed.

- Primary endpoints: PFS by BICR, OS (D + CT vs CT)
- Key secondary endpoints: PFS by BICR, OS, OS in pts with bTMB ≥20 mut/Mb (D + T + CT vs CT)
- Other secondary endpoints: ORR, DoR, BOR by BICR; 12-mo PFS; HRQoL; safety/tolerability

Johnson. WCLC 2021. Abstr PL02.01.

CheckMate 227

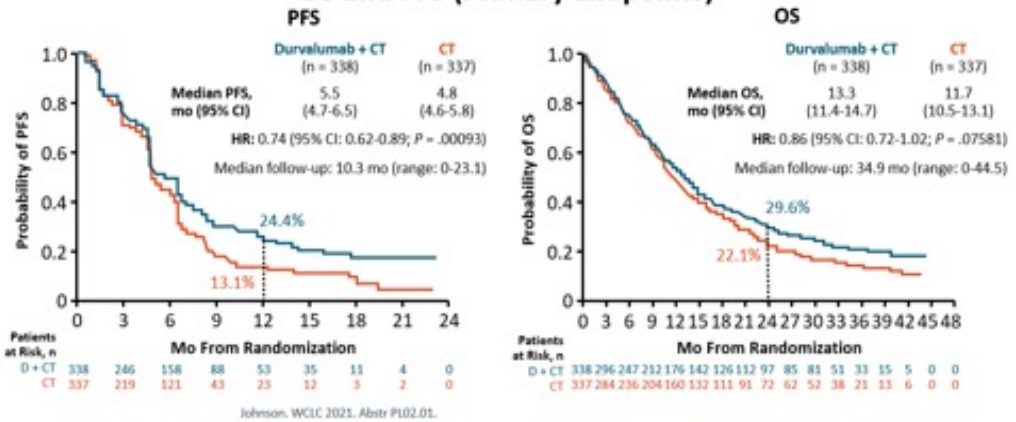
4-Yr OS by PD-L1 Expression



Paz-Ares. ASCO 2021. Abstr 9016.

POSEIDON

OS and PFS (Primary Endpoints)



Johnson. WCLC 2021. Abstr PL02.01.

CheckMate 9LA

Nivolumab/Ipilimumab + Chemotherapy in Advanced NSCLC

- Randomized, open-label, phase III study

Stratified by PD-L1 expression (≥1% vs <1%†), sex, and histology (squamous vs nonsquamous)*

Patients with stage IV or recurrent NSCLC, no previous systemic tx, no sensitizing *EGFR/ALK* alterations, ECOG PS 0/1 (N = 719)

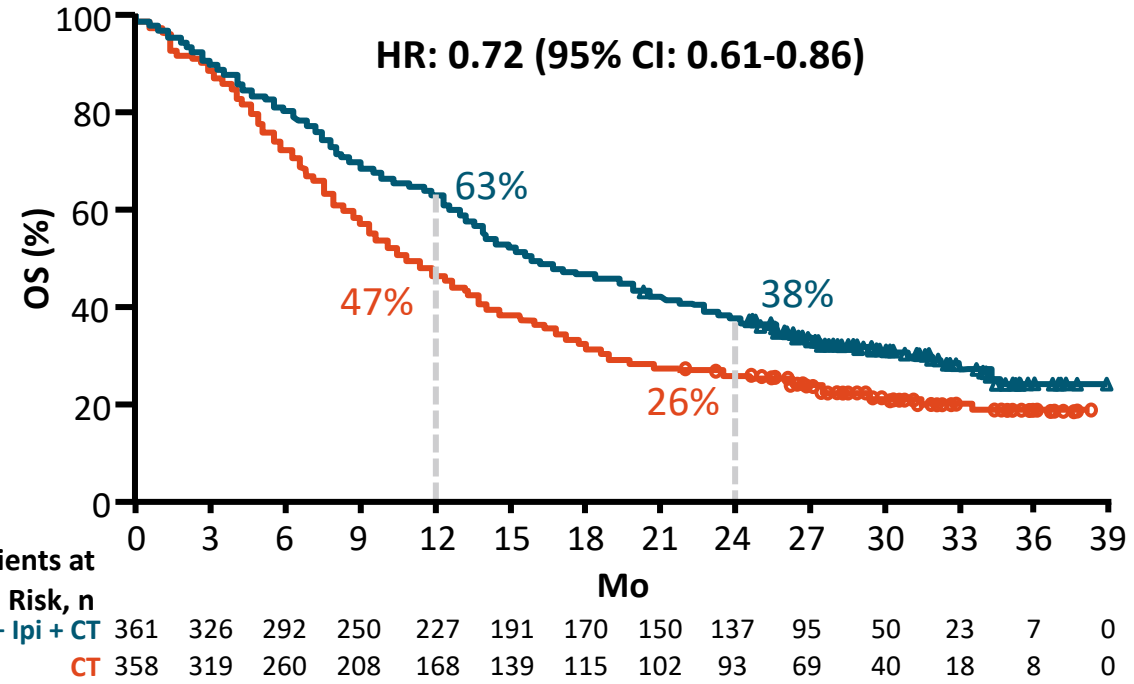
NIVO 360 mg Q3W + **IPI** 1 mg/kg Q6W + **CT**‡ Q3W (2 cycles) (n = 361)

CT‡ Q3W (4 cycles) Optional pemetrexed maintenance (NSQ) (n = 358)

Until PD, unacceptable toxicity, or for 2 yr for IO

*PD-L1 assessed by 28-8 IHC assay. †Patients unevaluable for PD-L1 were stratified to PD-L1 <1% and capped to 10% of all randomized patients. ‡NSQ: platinum + pemetrexed; SQ: carboplatin + nab-paclitaxel.

	Nivo + Ipi + CT (n = 361)	CT (n = 358)
Median OS, mo (95% CI)	15.8 (13.9-19.7)	11.0 (9.5-12.7)



- Regimen approved by FDA in May 2020
- DoR: 11.3 mo with nivolumab/ipilimumab + CT vs 5.6 mo with CT alone

Reck. ASCO 2021. Abstr 9000.

Immunotherapy Options for Advanced NSCLC

High PD-L1 Expression Across Histologies

Parameter	KEYNOTE-024: Pembrolizumab (n = 154)[1]	IMpower110: Atezolizumab (n = 107)[2]	EMpower-Lung 1: Cemiplimab (n = 283)[3]	CheckMate 227: Nivo/Ipi (n = 205)[4]	CheckMate 9LA: Nivo/Ipi + CT (n = 76)[5]
PD-L1+ definition	TPS ≥50%*	TC3 or IC3†	TPS ≥50%*	TPS ≥50%‡	TPS ≥50%‡
ORR, %	46.1	40.2	39.0	45.4	50.0
Median DoR, mo	29.1	38.9	16.7	31.8	26.0
Median PFS, mo	7.7 (HR: 0.50)	8.2 (HR: 0.59)	8.2 (HR: 0.54)	6.7 (HR: 0.60)	7.5 (HR: 0.59)
Median OS, mo	26.3 (HR: 0.62)	20.2 (HR: 0.76)	NR (HR: 0.57)	21.2 (HR: 0.66)	18.9 (0.67)

*By PD-L1 22C3 IHC assay.

†Staining of ≥50% tumor cells (TC3) or ≥10% tumor-infiltrating immune cells (IC3) by PD-L1 SP142 IHC assay.

‡PD-L1 28-8 IHC assay.

1. Reck. JCO. 2021;39:2339. 2. Jassem. J Thorac Oncol. 2021;[Epub]. 3. Sezer. Lancet. 2021;397:592. 4. Paz-Arez. ASCO 2021. Abstr 9016. 5. Reck. ASCO 2021. Abstr 9000.

Immunotherapy Options for Advanced NSCLC

PD-L1 Expression Negative Across Histologies

Outcome Across Histologies	CheckMate 227: Nivo/Ipi (n = 187)[1]	CheckMate 9LA: Nivo/Ipi + CT (n = 135)[2]
ORR, %	27.3	31.1
Median DoR, mo	18.0	17.5
Median PFS, mo (HR)	5.1 (0.74)	5.8 (0.68)
Median OS, mo (HR)	17.2 (0.64)	17.7 (0.67)

OS for Nonsquamous	CheckMate 227: Nivo/Ipi[1]	CheckMate 9LA: Nivo/Ipi + CT[2]	KEYNOTE-189: Pembro + CT[3]
Median OS, mo (HR)	17.5 (0.69)	Not reported (0.75)	17.2 (0.51)
2-yr OS, %	25	38	39

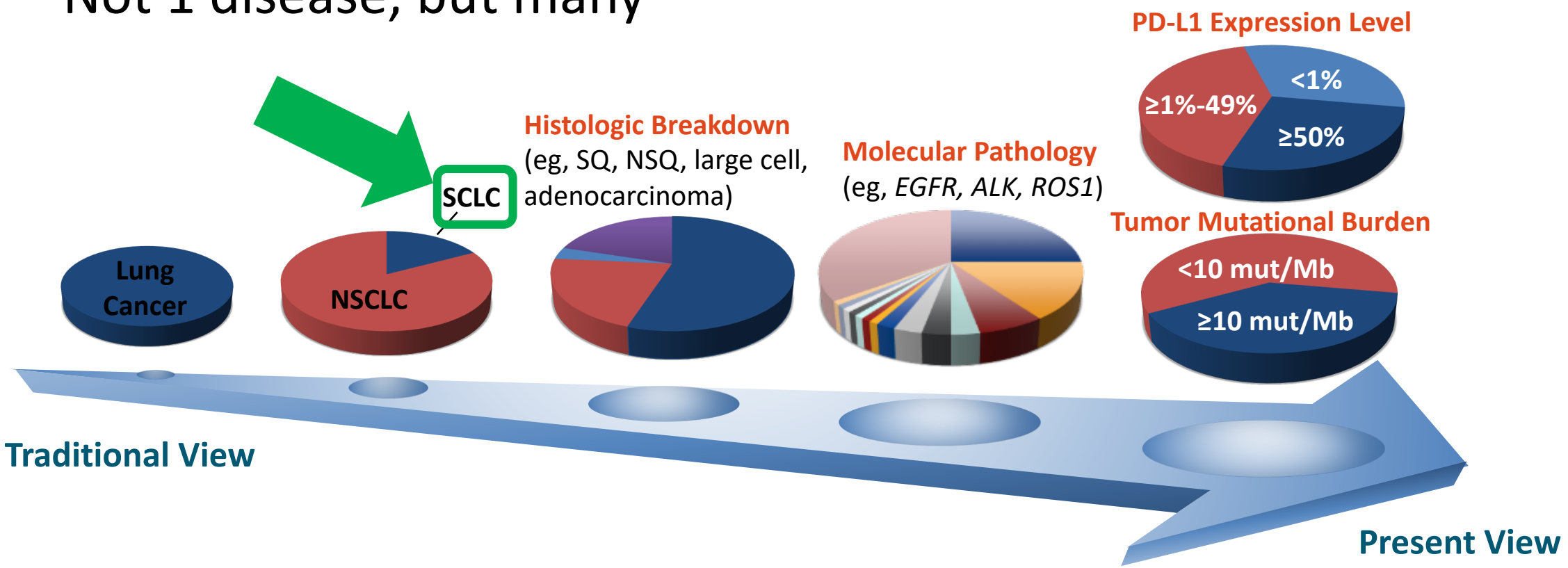
OS for Squamous	CheckMate 227: Nivo/Ipi[1]	CheckMate 9LA: Nivo/Ipi + CT[2]	KEYNOTE-407: Pembro + CT[4]
Median OS, mo (HR)	15.9 (0.53)	Not reported (0.48)	15.0 (0.79)
2-Yr OS, %	22	33	30

1. Paz-Arez. ASCO 2021. Abstr 9016. 2. Reck. ASCO 2021. Abstr 9000.
3. Rodríguez-Abreu. Ann Oncol. 2021;32:881. 4. Paz-Ares. J Thorac Oncol. 2020;15:1657.

Evolution of Therapy in Lung Cancer

Small Cell Lung Cancer (SCLC)

- Not 1 disease, but many



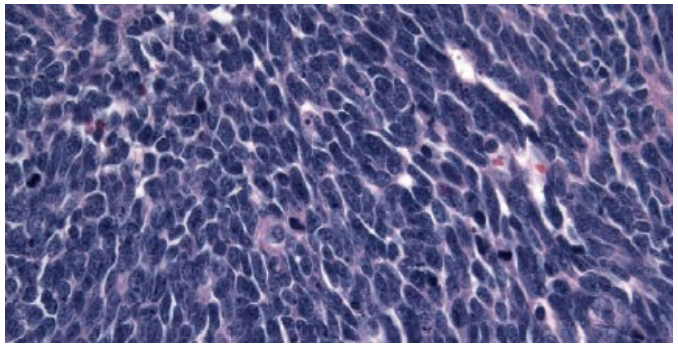
Cooper. Pathology. 2011;43:103. Langer. JCO. 2010;28:5311. Galon. Immunity. 2013;39:11.
Pao. Lancet Oncol. 2011;12:175. Krigsfeld. AACR 2017. Abstr CT143. Hellmann. NEJM. 2018;378:2093.

SCLC Pathology

Spectrum of Neuroendocrine Carcinomas (NEC)

- SCLC presents as malignant, epithelial, high-grade, neuroendocrine tumors[1,2]
  - Markers of epithelial origin
  - Neuroendocrine and neural differentiation markers: synaptophysin, chromogranin A, CD56
- SCLC falls along spectrum of WHO classification of neuroendocrine lung tumors[2,3]
- Potential therapeutic Implications

HPF View of SCLC Tumor[1]



WHO Classification[2,3]	Mitoses/ 10 HPF	Necrosis	Cytologic Features
Typical carcinoid	< 2	None	--
Atypical carcinoid	2-10	Generally punctate	--
Small-cell carcinoma	> 10	Generally abundant	Small size, scant cytoplasm, finely granular chromatin, faint nucleoli
Large-cell neuroendocrine carcinoma	> 10	Generally abundant	Cytologic features opposite SCLC

1. Jackman DM, et al. Lancet. 2005;366:1385-1396. 2. WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart. 2015. 3. Rossi G, et al. Curr Opin Pulm Med. 2014;20:332-339.

SCLC

Staging

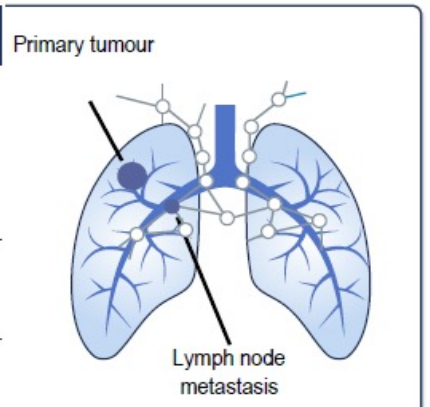
The VALSG system classifies SCLC as either limited or extensive:[2]

Limited stage

Disease confined to one hemithorax
- ± Regional lymph node metastases
- ± Pleural effusions independent of cytology

Often confined to an area that can be encompassed within a radiation port

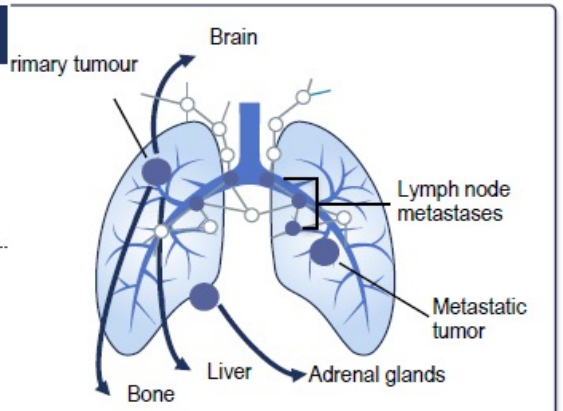
Corresponds to stages I–III
(T any, N any, M0)



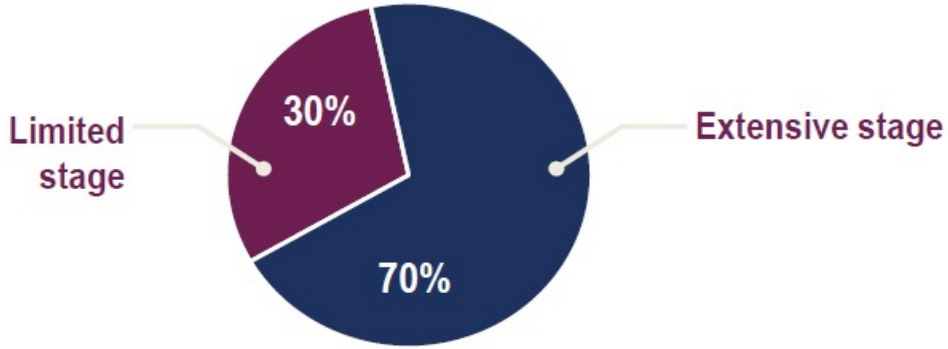
Extensive stage

Any disease at sites beyond the definition of limited disease

Corresponds to stage IV
(T any, N any, M1a/b)[a]



SCLC is predominantly diagnosed in advanced stages[3]



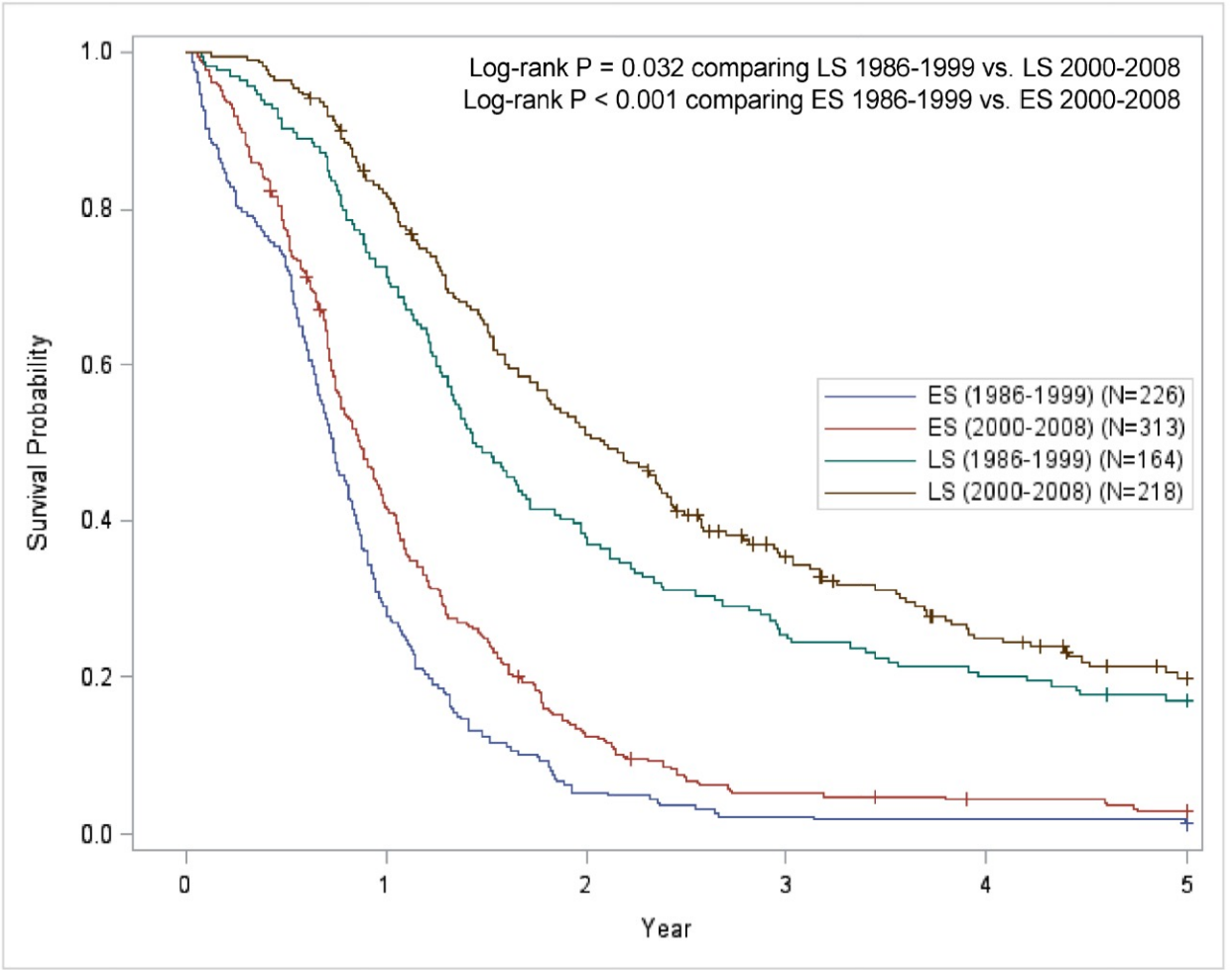
- [a]Or T3–4 owing to multiple lung nodules that are too extensive or have tumoural/nodal volume that is too large to be encompassed in a tolerable radiation plan[4]
- SCLC, small-cell lung cancer; TNM, tumour, node, metastasis; VALSG, Veterans Administration Lung Study Group
- 1. Farago AF, et al. *Transl Lung Cancer Res* 2018;7:69–79; 2. Stahel RA, et al. *Lung Cancer* 1989;5:119–126; 3. National Cancer Institute. Small Cell Lung Cancer Treatment (PDQ®) – Health Professional Version. Available at: https://www.cancer.gov/types/lung/hp/small-cell-lung-treatment-pdq (Accessed November 2020);
4. National Comprehensive Cancer Network. Inc. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Small Cell Lung Cancer version 2.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/sclc_blocks.pdf (Accessed November 2020)

SCLC

Prognosis

Median survival time and 1-year, 2.5-year, and 5-year survival rate for each time-period[3]

	1986 to 1999 (N = 410)	2000 to 2008 (N = 593)[3]	P-value[2]
Median survival time, months (95% CI) [1]			
Overall	11.3 (10.5 – 12.7)	15.2 (13.6 – 16.6)	
By stage			
Limited	17.3 (15.7 – 20.6)	25.1 (21.1 – 28.8)	
Extensive	8.8 (7.9 – 9.8)	10.4 (9.2 – 11.6)	
Not classifiable	16.1 (10.0 – 38.2)	26.1 (20.0 – 32.9)	
1-year survival rate, %			
Overall	48.1	60.1	**< 0.001**
By stage			
Limited	72.6	82.0	**0.022**
Extensive	28.8	41.8	**0.001**
Not classifiable	65.0	81.8	0.172
2.5-year survival rate, %			
Overall	15.9	22.6	**< 0.001**
By stage			
Limited	31.1	40.7	**0.009**
Extensive	3.6	6.8	**< 0.001**
Not classifiable	30.0	44.6	0.162
5-year survival rate, %			
Overall	8.3	11.1	**< 0.001**
By stage			
Limited	17.1	19.9	**0.032**
Extensive	1.3	2.8	**< 0.001**
Not classifiable	15.0	26.1	0.178



Schabath MB. Lung Cancer. 2014 Oct;86(1):14-21

Extensive-Stage SCLC

First-line Chemotherapy

- SoC: cisplatin/carboplatin and etoposide for 4-6 cycles[1]
  - Response rates: ~ 50% to 75%
  - 2-yr OS: < 5%
  - Median OS: 9-11 mos
- Cisplatin vs. Carboplatin
  - Meta-analysis (N = 663)[2]
  - No differences in OS, PFS, ORR
- Irinotecan
  - superior to etoposide in Japan
  - Results not replicated in two US studies
- Pemetrexed
  - inferior to etoposide
- Inevitably, all patients progress: Recurrent Disease!

Historic Management of SCLC

- Improving systemic therapy
  - Alternating "non-cross resistant" regimens
  - Maintenance
  - Dose escalation
  - Dose-intense regimens
  - Hematopoietic GFS
  - Two vs. more drugs
  - Four vs. six (more) cycles
  - Cisplatin vs. Carboplatin
  - Combinations with new drugs

1. Bernhardt EB, et al. Cancer Treat Res. 2016;170:301-322. 2. Rossi A, et al. J Clin Oncol. 2012;30:1692-1698. 3. Noda K, et al. N Engl J Med. 2002;346:85-91. 4. Hanna N, et al. J Clin Oncol. 2006;24:2038-2043.

Extensive-Stage SCLC:
"First-line" Radiation – PCI, Consolidation XRT

- PCI is guideline-recommended for pts in CR or PR; however, its use remains controversial
  - 2007: reduction in risk of brain metastases, improvement in median OS and 1-yr OS[1]
  - 2017: no improvement in OS with PCI vs observation[2]

REMAINS CONTROVERSIAL

- Thoracic RT following PCI provides OS benefit at 2 yrs[3]
  - 498 pts with response to first-line chemotherapy received PCI followed by randomization to TRT or no further therapy
    - 1-yr OS: 33% vs 28% (NS)
    - 2-yr: OS: 13% vs 3% (*P* = .001)

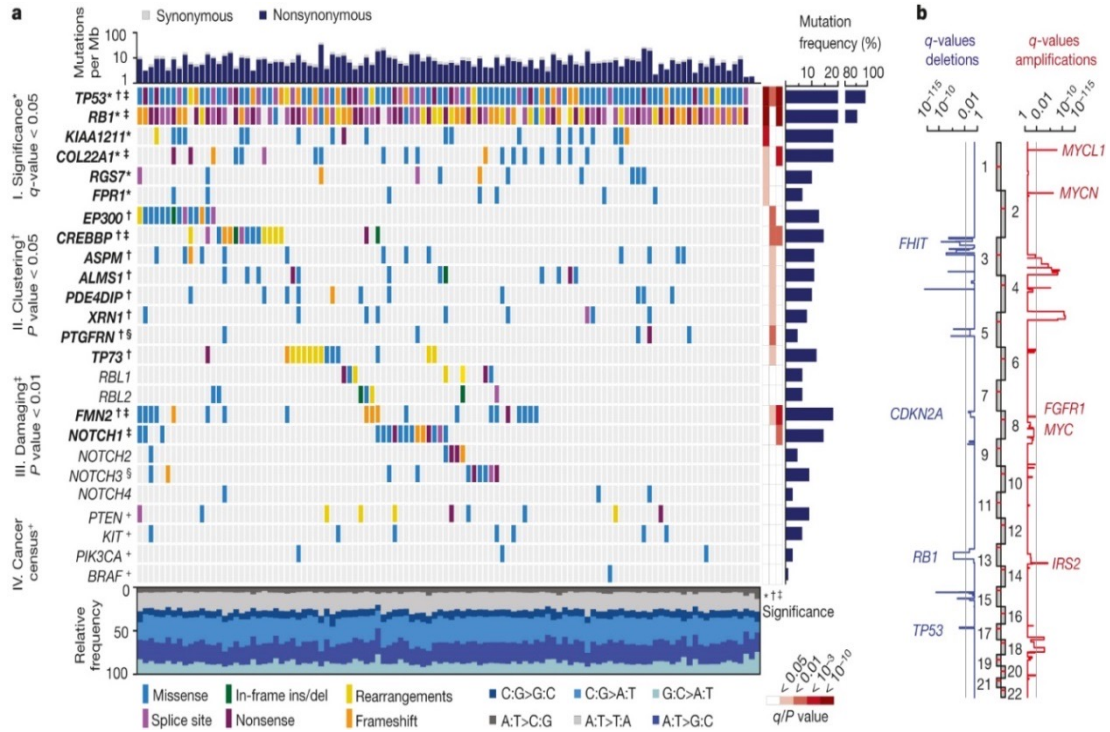
NOT WIDELY ADOPTED

1. Slotman B, et al. N Engl J Med. 2007;357:664-672. 2. Takahashi T, et al. Lancet Oncol. 2017;18:663-671. 3. Slotman BJ, et al. Lancet. 2015;385:36-42.

Genetic Alterations in SCLC

No Clear Targetable Oncogenic Driver

- Nearly all tumors have loss or inactivation of *TP53* and *RB1*[1-4]
- *MYC* family member amplification is common[1-4]
  - *MYC-L1* > *N-MYC* > *C-MYC*[1]
  - Recurrent *RFL-MYCL1* fusions have been described[4]
- Additional alterations include:
  - *FGFR1* amplification (6%)[1]
  - *SOX2* amplification (27%)[4]
  - Recurrent point mutations in chromatin modifiers: *CREBBP, EP300, MLL* (~ 10-20%)[1,2]
  - Inactivating mutations in *NOTCH* family genes (25%)[2]
  - *EZH2,* regulator of chromatin remodeling implicated in acquired resistance[3]



1. Peifer M, et al. Nat Genet. 2012;44:1104-1110. 2. George J, et al. Nature. 2015;524:47-53. 3. Sabari JK, et al. Nat Rev Clin Oncol. 2017;14:549-561. 4. Rudin CM, et al. Nat Genet. 2012;44:1111-1116.

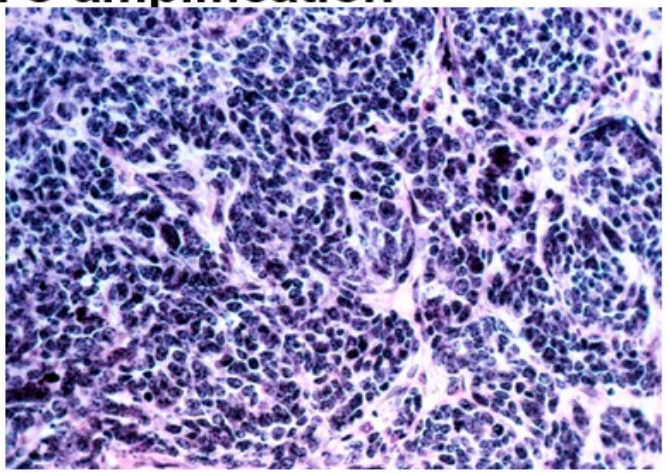
Genetic Alterations in SCLC

No Clear Targetable Oncogenic Driver

Replication Stress, DDR and Genomic Instability

SCLC Tumor Profile:

- **Mutation or loss of both TP53 and RB1**
- **High expression of ATM, ATR, CHK1, and CHK2, CDC25A, B, & C (relative to NSCLC)**
- **MYC amplification**

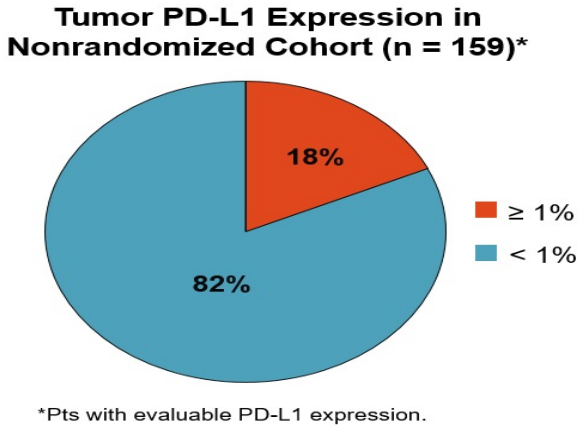


Net Effect

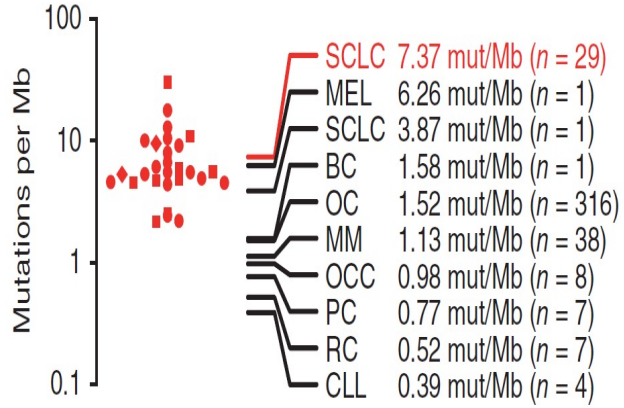
- Rapidly dividing tumor under immense replicative stress
- Dependence on robust DNA damage response (DDR) to maintain survival
- High level of genomic instability

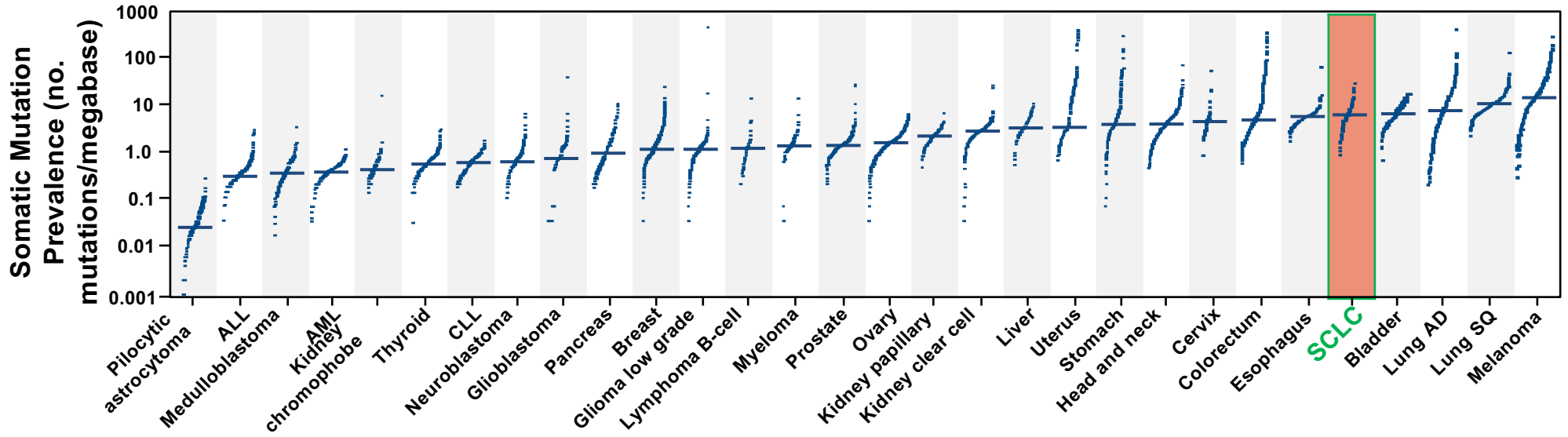
Immunotherapy and SCLC

PD-L1 expression and TMB



PD-L1 Expression	ORR, % (n/N)	
	Nivolumab (n = 98)	Nivolumab + Ipilimumab (n = 61)
< 1%	14 (9/64)	32 (10/31)
≥ 1%	9 (1/11)	10 (1/10)



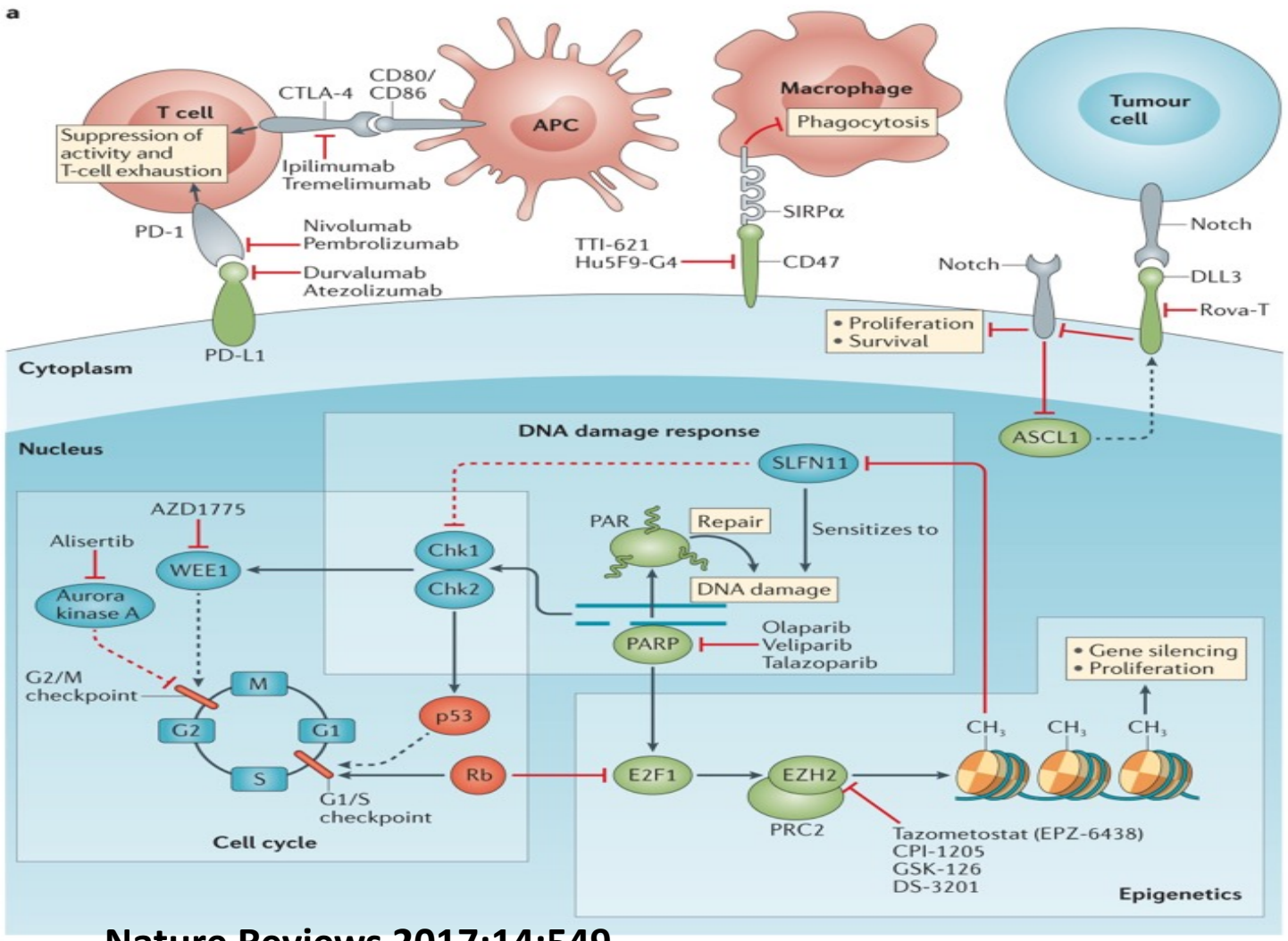


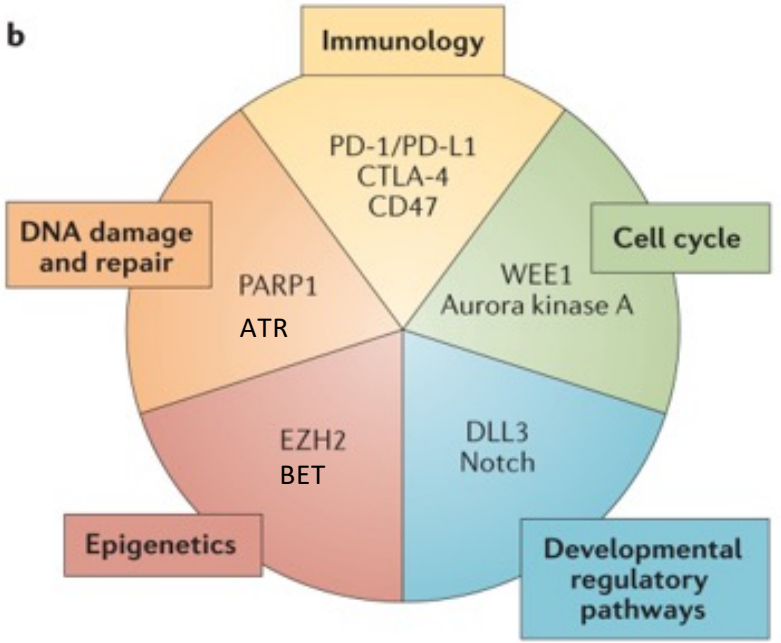
High mutational burden seen in SCLC

Hellmann MD, et al. ASCO 2017. Abstract 8503. Peifer. Nat Genet. 2012;44:1104. Alexandrov. Nature. 2013;500:415.

SCLC Systemic Therapy

Current Areas of Advances





Signalling pathways and physiological domains that are the focus of experimental targeted therapies for small-cell lung cancer (SCLC).
a | Dashed and solid lines indicate indirect and direct interactions, respectively. Proteins in green are typically upregulated in SCLCs compared with nonmalignant lung tissue, while those in red are downregulated or absent. Examples of the investigational molecularly targeted agents or antibody-based treatments targeting each signalling node are provided

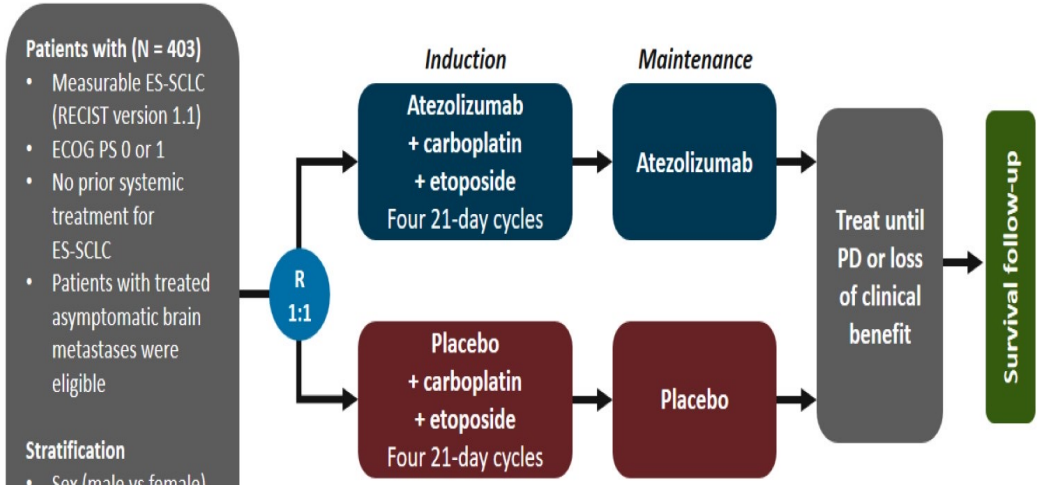
Nature Reviews 2017;14:549

ES-SCLC Immunotherapy

New First Line Standard

First-Line Treatment: IMpower133

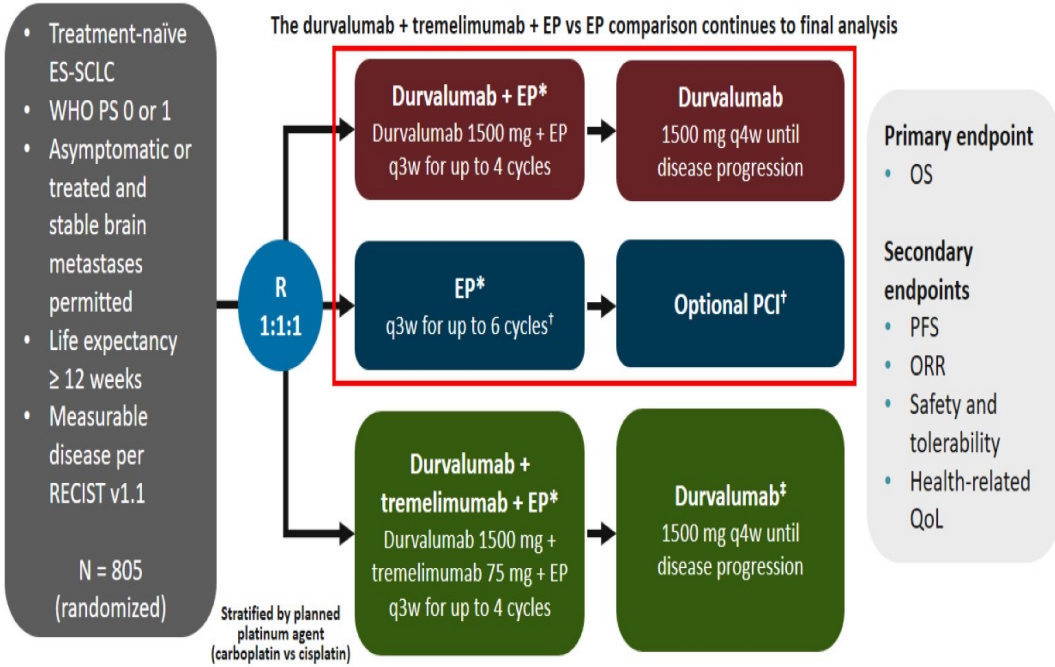
Study Design



Note: Atezolizumab, 1200 mg IV, Day 1; Carboplatin, AUC 5 mg/mL/min IV, Day 1; Etoposide, 100 mg/m 2 IV, Days 1–3.
*Only patients with treated brain metastases were eligible.
Horn L, et al. *N Engl J Med*. 2018;379:2220-2229; Reck M, et al. ESMO 2019. Presentation 1736O.

First-Line Treatment: CASPIAN

Study Design



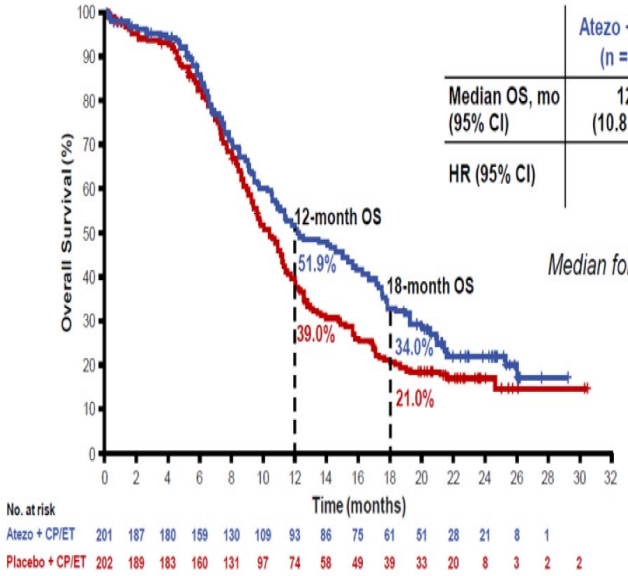
*EP consists of etoposide 80–100 mg/m^2 with either carboplatin AUC 5-6 or cisplatin 75-80 mg/m^2; †Patients could receive an additional 2 cycles of EP (up to 6 cycles total) and PCI at the investigator's discretion; ‡Patients received an additional dose of tremelimumab post-EP.
Paz-Ares L, et al. *Lancet*. 2019;394:1929-1939; Paz-Ares L, et al. WCLC 2019. Presentation PL02.11.

ES-SCLC Chemo-Immunotherapy

New First Line Standard

First-Line Treatment: IMpower133

Updated Results



	Atezo + CP/ET (n = 201)	Placebo + CP/ET (n = 202)
Median OS, mo (95% CI)	12.3 (10.8, 15.8)	10.3 (9.3, 11.3)
HR (95% CI)	0.76 (0.60, 0.95) p = 0.0154[a]	

Median follow-up, 22.9 months

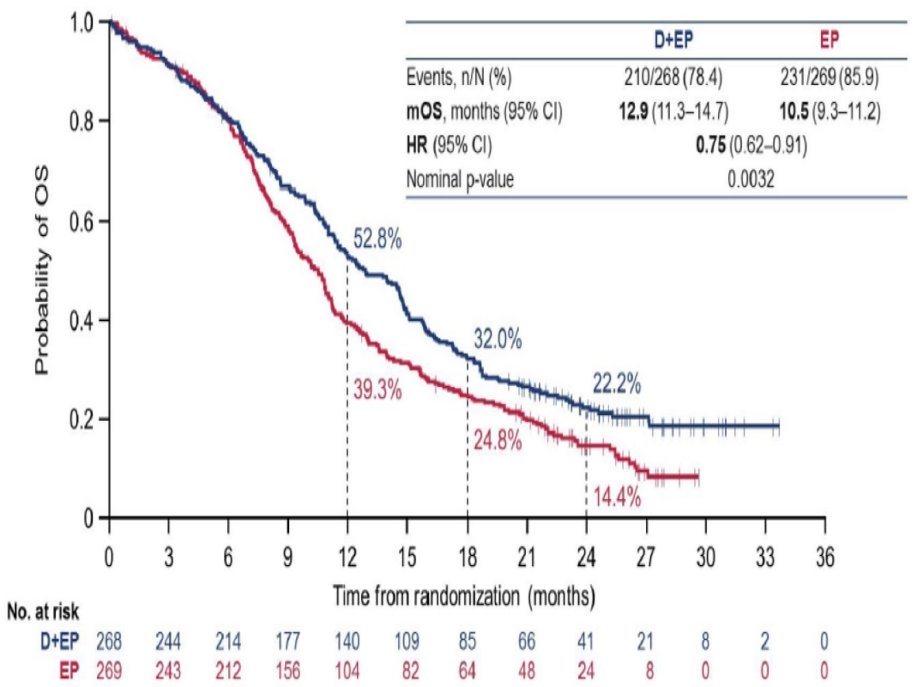
[a]p-value is provided for descriptive purpose.
CCOD 24 January 2019

Endpoint	Atezo + CP/ET (n = 201)	Placebo + CP/ET (n = 202)
ORR, %	60.2	64.4
mDOR, mo	4.2	3.9

Reck M, et al. ESMO 2019. Presentation 1736O.

First-Line Treatment: CASPIAN

Updated OS



	D+EP	EP
Events, n/N (%)	210/268 (78.4)	231/269 (85.9)
mOS, months (95% CI)	**12.9** (11.3–14.7)	**10.5** (9.3–11.2)
HR (95% CI)	**0.75** (0.62–0.91)	
Nominal p-value	0.0032	

Paz-Ares L, et al. ASCO® 2020. Presentation 9002.

Maintenance Ipi-Nivo

CheckMate 451

- Randomized, double-blind phase III trial

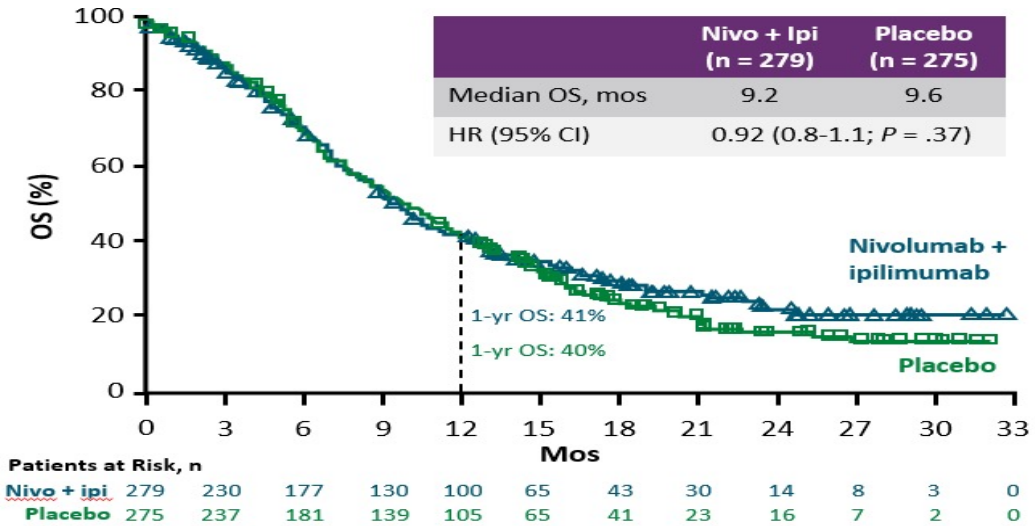
Stratified by ECOG PS (0 vs 1), previous PCI (yes vs no), sex (male vs female)

Patients with ED-SCLC, ECOG PS 0/1, at least SD following 4 cycles of first-line platinum-based CT, no symptomatic CNS mets, (N = 834)

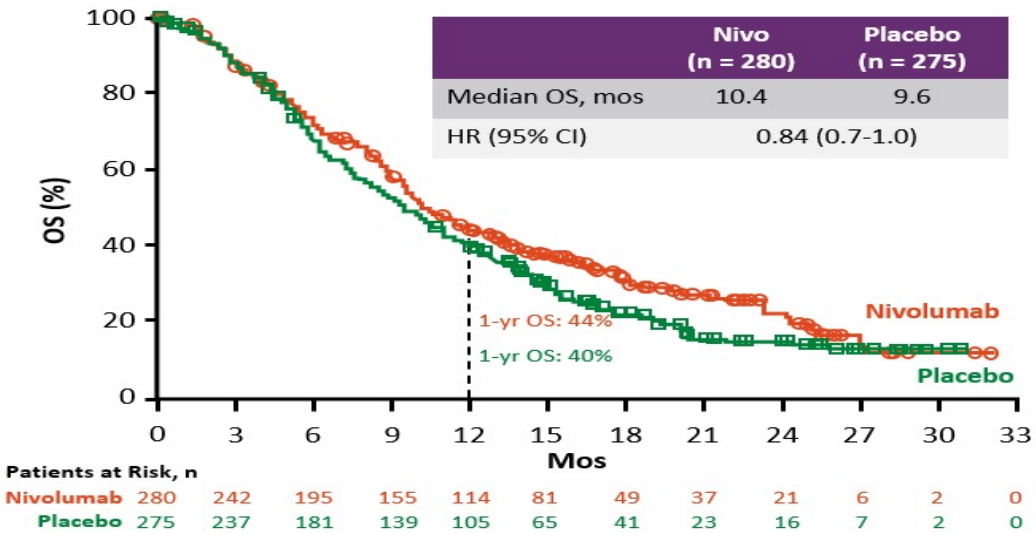
- **Nivolumab** 1 mg/kg Q3W + **Ipilimumab** 3 mg/kg Q3W (max 4 doses) (n = 279)
- **Nivolumab** 240 mg Q2W
- **Nivolumab** 240 mg Q2W (n = 280)
- **Placebo** (n = 275)

→ *Treat until disease progression or unacceptable toxicity; maximum of 2 yrs*

- Primary endpoint: OS—nivolumab + ipilimumab vs placebo
- Secondary endpoints: OS—nivolumab vs placebo; PFS—nivolumab + ipilimumab and nivolumab vs placebo
- Exploratory endpoints: ORR, DoR, safety and tolerability



	Nivo + Ipi (n = 279)	Placebo (n = 275)
Median OS, mos	9.2	9.6
HR (95% CI)	0.92 (0.8-1.1; *P* = .37)	



	Nivo (n = 280)	Placebo (n = 275)
Median OS, mos	10.4	9.6
HR (95% CI)	0.84 (0.7-1.0)	

Owonikoko. ELCC 2019. Abstr LBA1. NCT02538666. Used with permission.

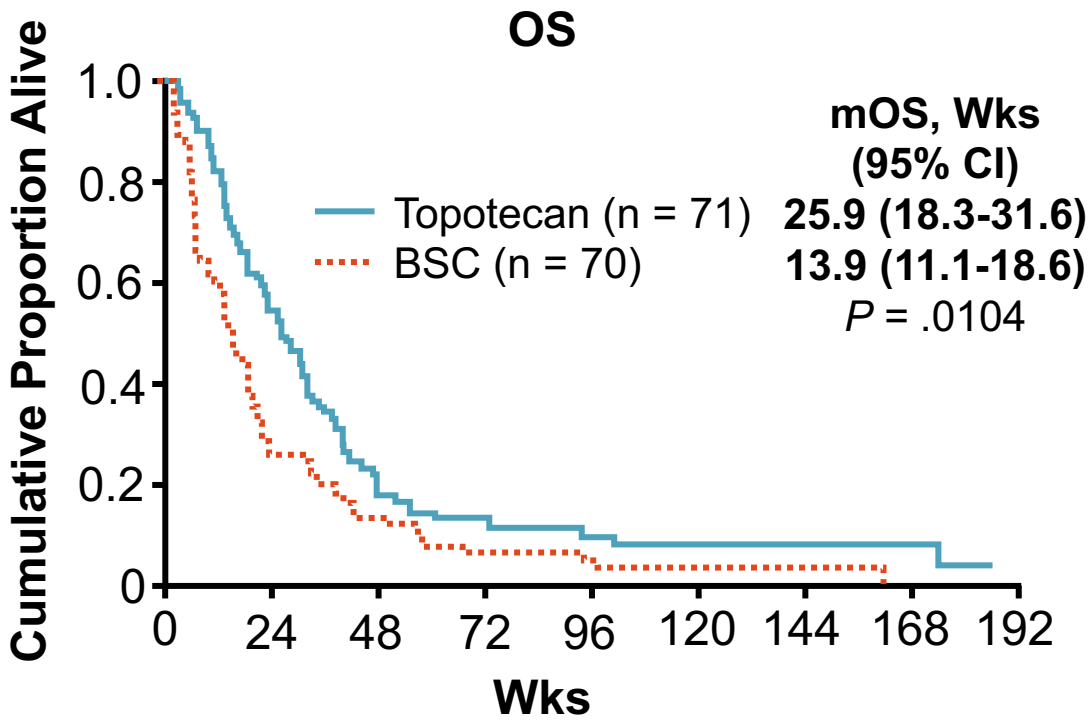
Management of Relapsed SCLC

Second-Line Topotecan

- Single-arm phase II study of second-line IV topotecan (N = 92)[1]
  - Overall median OS: 5.4 mos

Outcome	Refractory (n = 47)	Sensitive (n = 45)
ORR, % (95% CI)	6.4 (1.3-17.6)	37.8 (23.8-53.5)
Median OS, mos	4.7	6.9

- Randomized phase III trial of BSC ± oral topotecan in pts with relapsed SCLC (N = 141)[2]



1. Ardizzoni A, et al. J Clin Oncol. 1997;15:2090-2096. 2. O'Brien ME, et al. J Clin Oncol. 2006;24:5441-5447.

CheckMate 331

Nivolumab vs Topotecan/Amrubicin in Relapsed SCLC

- SCLC
- Recurrence/PD after 1L platinum CT or CRT (≥4 cycles)
- ECOG PS ≤1
- No symptomatic CNS metastases
- No prior therapy with anti–CTLA-4, anti–CD137, anti–PD-1/PD-L1/PD-L2

N = 480

1:1 R

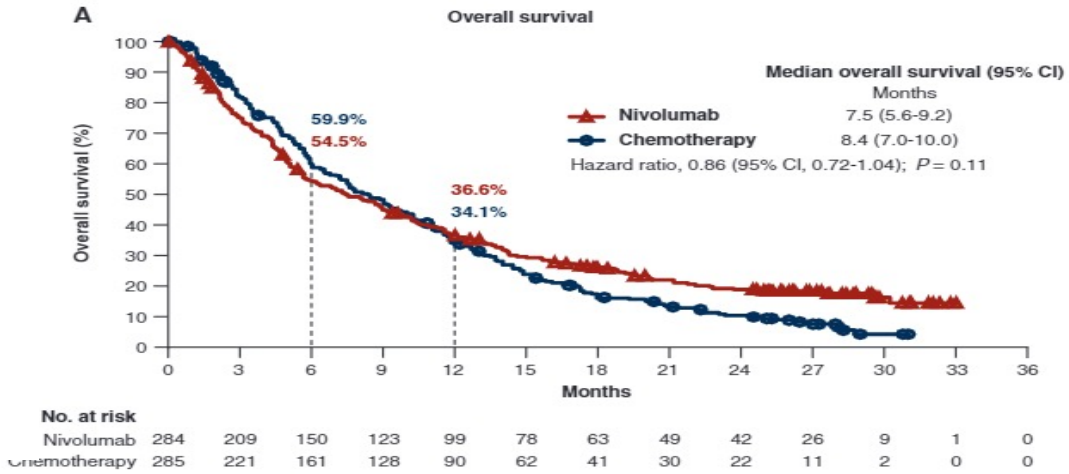
- Nivolumab
- Topotecan or amrubicin

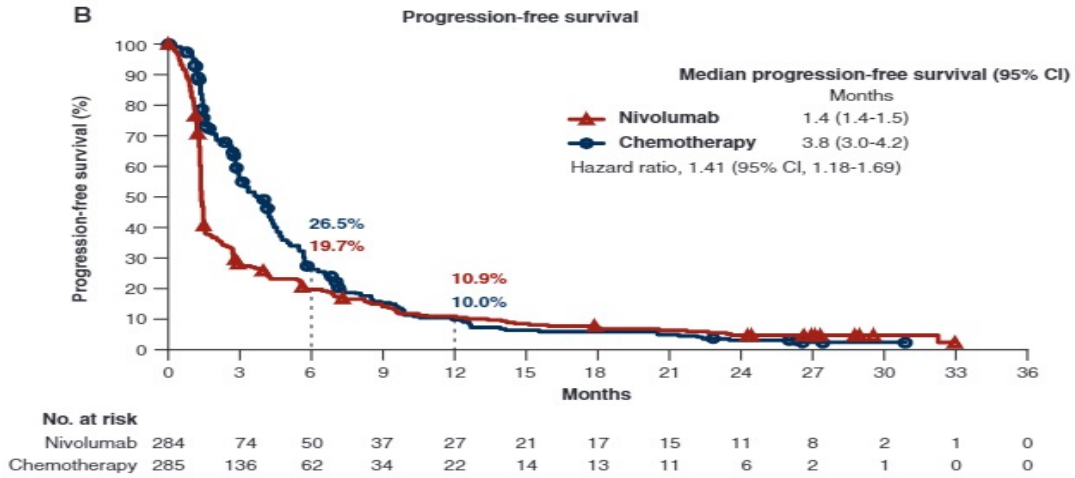
- **Primary outcome measure:** OS

1. Reck M et al. European Society for Medical Oncology 2018 Congress (ESMO 2018). Abstract 489.

Table 3. Summary of tumor response

	Nivolumab (*n* = 284)	Chemotherapy (*n* = 285)
Objective response[a]		
Patients with response, *n*	39	47
% of patients (95% CI)	13.7 (10.0-18.3)	16.5 (12.4-21.3)
Estimated odds ratio (95% CI)	0.80 (0.50-1.27)	
Duration of objective response, months[b]		
Median (95% CI)	8.3 (7.0-12.6)	4.5 (4.1-5.8)
Range	0.0+ to 31.7+	1.6-23.9
Best overall response, *n* (%)		
Complete response	1 (0.4)	1 (0.4)
Partial response	38 (13.4)	46 (16.1)
Stable disease	58 (20.4)	116 (40.7)
Progressive disease	150 (52.8)	67 (23.5)
Could not be determined	37 (13.0)	55 (19.3)





doi: 10.1016/j.annonc.2021.01.071. Epub 2021 Feb 1

Relapsed SCLC

Lurbinectidin (Phase II Basket Trial)

Lurbinectedin[a,b]

- Synthetic analog of trabectedin used to treat soft-tissue sarcoma
- Selective inhibitor of oncogenic transcription
  - Covalently binds CG-rich sequences mainly located near promoters; inhibits RNA Pol II associated to DNA and leads to its specific degradation
- May also influence the TM via processes, including suppression of immune cells (eg, TAMs)

Antitumor Activity

	Overall (n=105)
ORR, % (95% CI)	35.2 (26.2-45.2)
Best response	n (%)
- PR (confirmed)	37 (35.2) #
- SD	35 (33.3)
- PD	28 (26.7)
- NE* (non- evaluable)	5 (4.8)
Disease Control Rate,% (95% CI)	68.6 (58.8-77.3)

5 of 8 patients who failed prior immunotherapy had confirmed response

* Treatment discontinuation without any tumor assessment performed

	Resistant CTFI< 90 days (n=45)	Sensitive CTFI ≥ 90 days (n=60)
ORR, % (95% CI)	22.2 (11.2-37.1)	45.0 (32.1-58.4)
Best response (confirmed)	n (%)	n (%)
- PR	10 (22.2) #	27 (45.0) #
- SD	13 (28.9)	22 (36.7)
- PD	18 (40.0)	10 (16.7)
- NE* (non- evaluable)	4 (8.9)	1 (1.7)
Disease Control Rate), % (95% CI)	51.1 (35.8-66.3)	81.7 (69.6-90.5)

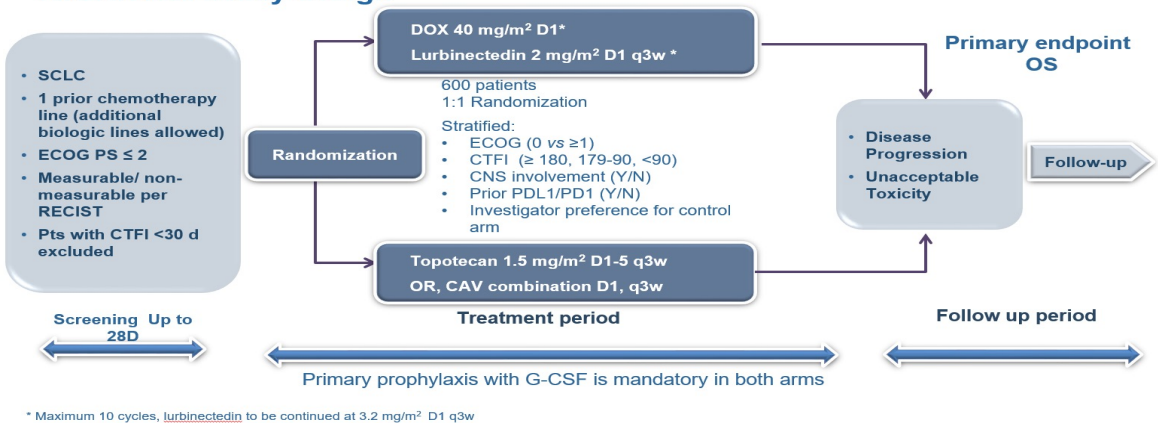
3 of 5 patients with resistant disease and 2 of 3 patients with sensitive disease who failed prior immunotherapy had confirmed response

* Treatment discontinuation without any tumor assessment performed

Phase III ATLANTIS Trial

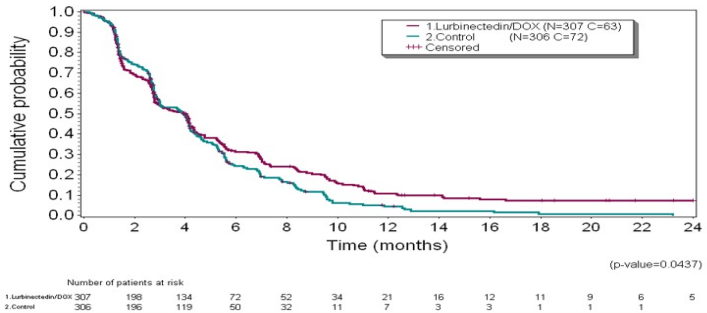
OS and PFS

ATLANTIS: Study design



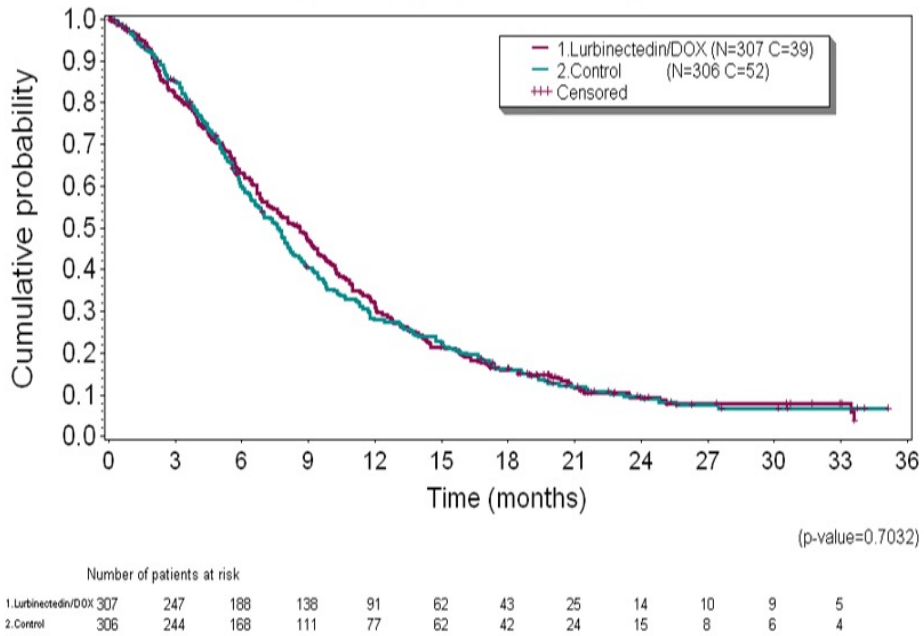
* Maximum 10 cycles, lurbinectedin to be continued at 3.2 mg/m² D1 q3w

PFS by IRC:



	Lurbinectedin+DOX (N=307)	Control (N=306)	Parameter	p-value
Events, n (%)	244 (79.5)	234 (76.5)		
Censored, n (%)	63 (20.5)	72 (23.5)		
Median PFS (95% CI), months	4.0 (2.8, 4.2)	4.0 (3.0, 4.1)	HR: 0.831 (0.693, 0.996)	0.0437
Mean PFS, months	5.9	4.6		
PFS (%) at 6 months (95% CI)	31.3 (25.8, 36.9)	24.4 (19.1, 30.1)		0.0851
PFS (%) at 12 months (95% CI)	10.8 (7.1, 15.3)	4.4 (2.1, 8.1)		0.0129

Overall Survival (ITT population)



	Lurbinectedin+DOX (N=307)	Control (N=306)	Parameter	p-value
Events, n (%)	268 (87.3)	254 (83.0)		
Censored, n (%)	39 (12.7)	52 (17.0)		
Median OS (95% CI), months	8.6 (7.1, 9.4)	7.6 (6.6, 8.2)	HR : 0.967 (0.815, 1.148)	0.7032
Mean OS, months	10.6	9.9		

IASLC WCLC 2021 Plenary

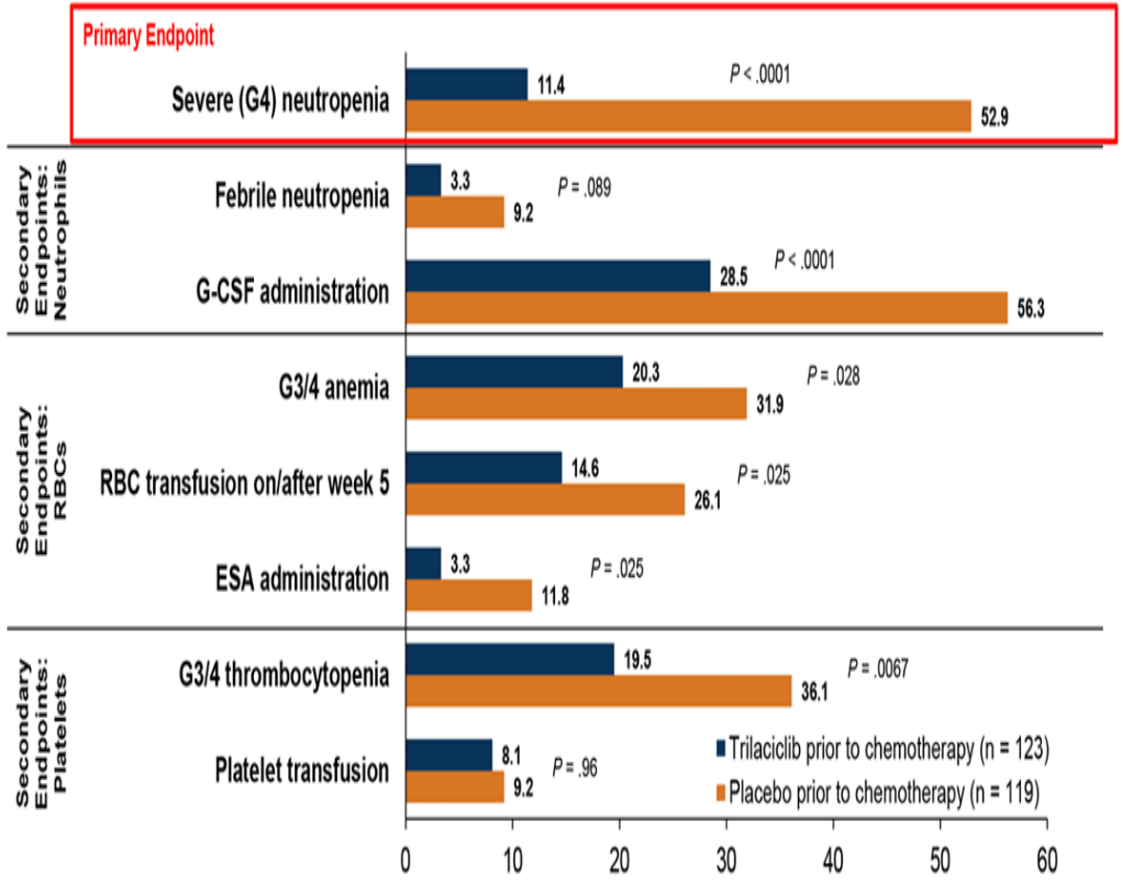
Trilaciclib

Randomized Trials – Pooled data

Trilaciclib, a First-in-Class Myelopreservation Agent, Proactively Reduces Risks Associated with Myelosuppressive Chemotherapy

Study	Patient Population	Treatment Schedule
G1T28-05 (NCT03041311)[1]	Newly diagnosed (first-line) ES-SCLC	Trilaciclib 240 mg/m^2 IV QD prior to chemotherapy on days 1-3 of each 21-day E/P/A IV cycle for up to four cycles, followed by atezolizumab monotherapy (without trilaciclib) Q21D Placebo IV QD prior to chemotherapy on days 1-3 of each 21-day E/P/A IV cycle for up to four cycles, followed by atezolizumab monotherapy (without placebo) Q21D
G1T28-02 (NCT02499770)[2]	Newly diagnosed (first-line) ES-SCLC	Trilaciclib 240 mg/m^2 IV QD prior to chemotherapy on days 1-3 of each 21-day E/P IV cycle Placebo IV QD prior to chemotherapy on days 1-3 of each 21-day E/P IV cycle
G1T28-03 (NCT02514447)[3]	Previously treated (second-/third-line) ES-SCLC	Trilaciclib 240 mg/m^2 IV QD prior to topotecan 1.5 mg/m^2 IV QD on days 1-5 of each 21-day cycle Placebo IV QD prior to topotecan 1.5 mg/m^2 IV QD on days 1-5 of each 21-day cycle

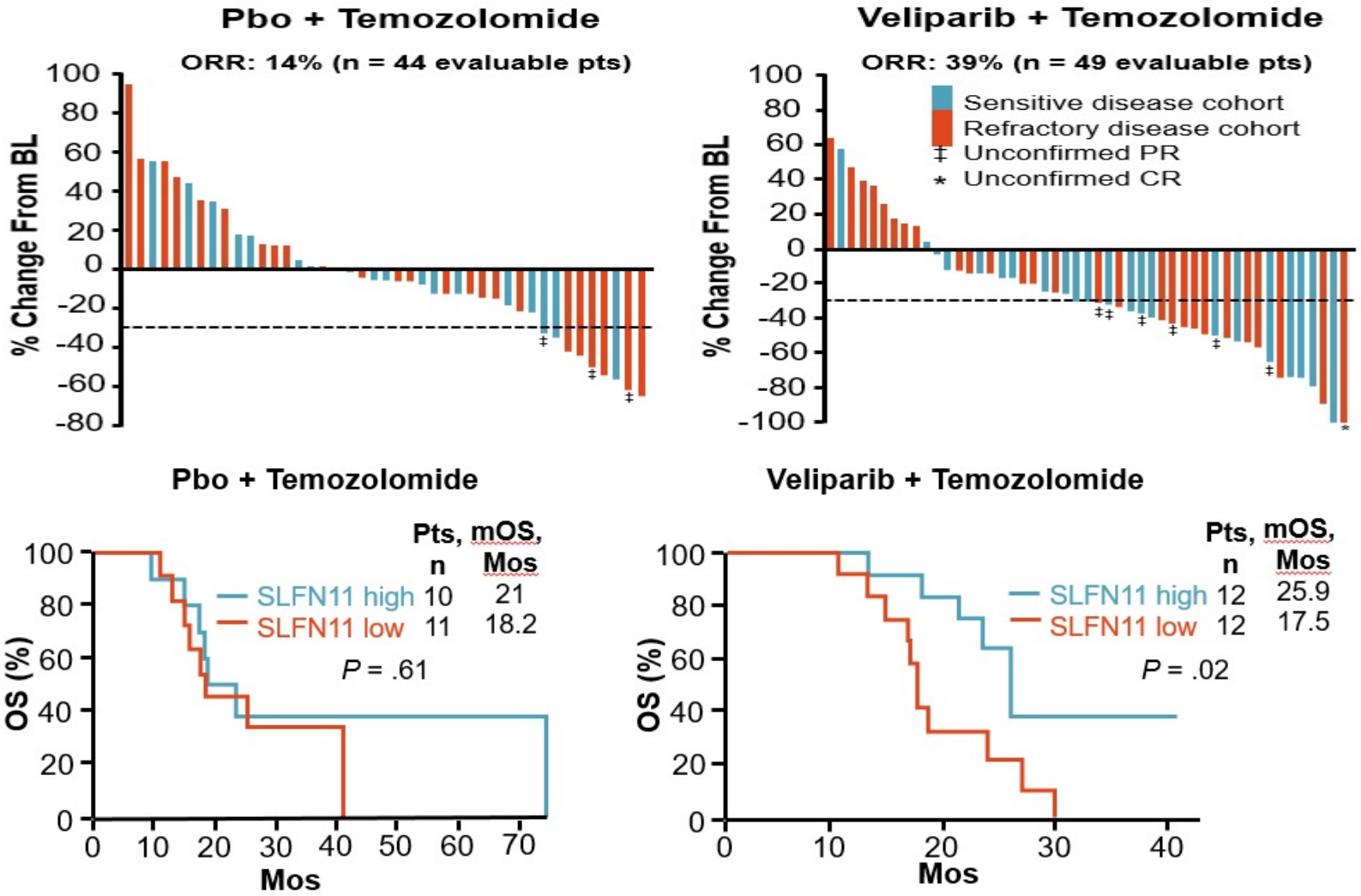
1. https://clinicaltrials.gov/ct2/show/NCT03041311. 2. https://clinicaltrials.gov/ct2/show/NCT02499770. 3. https://clinicaltrials.gov/ct2/show/NCT02514447.



1. Weiss J et al. *Clin Lung Cancer*. 2021 Mar 26 [Epub ahead of print].

Relapsed SCLC

Veliparib +/- Temozolomide: ORR and OS in Pts With SLFN11 Expression



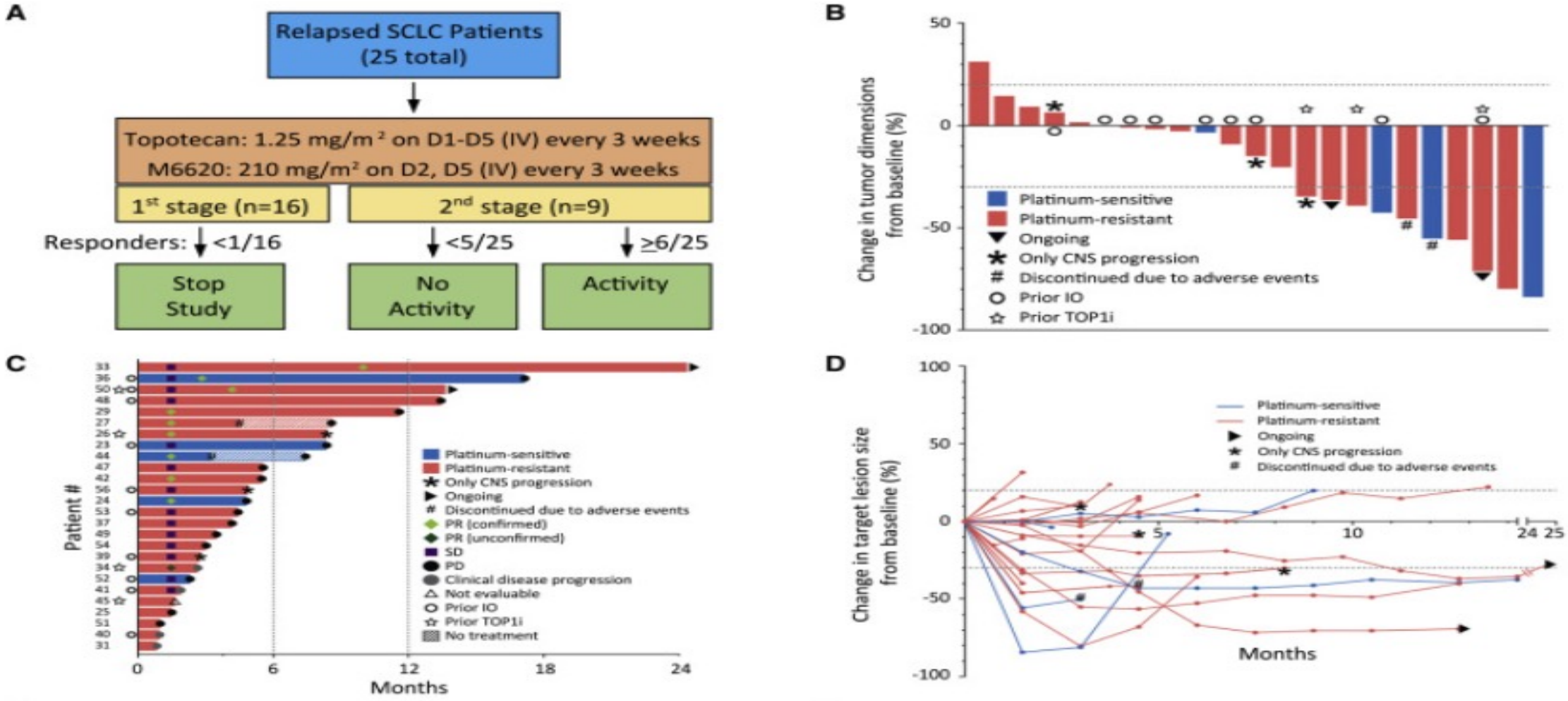
- Significantly better ORR with veliparib (*P* = .016)
- No significant difference in 4-mo PFS, mPFS, or mOS between arms
- Greater incidence of hematologic toxicities with veliparib combination

- SLFN11, a DDR protein, is aberrantly expressed in SCLC
- Veliparib: Trend toward better OS with higher tumor SLFN11 expression

Pietanza MC, et al. ASCO 2016. Abstract 8512.

Relapsed SCLC

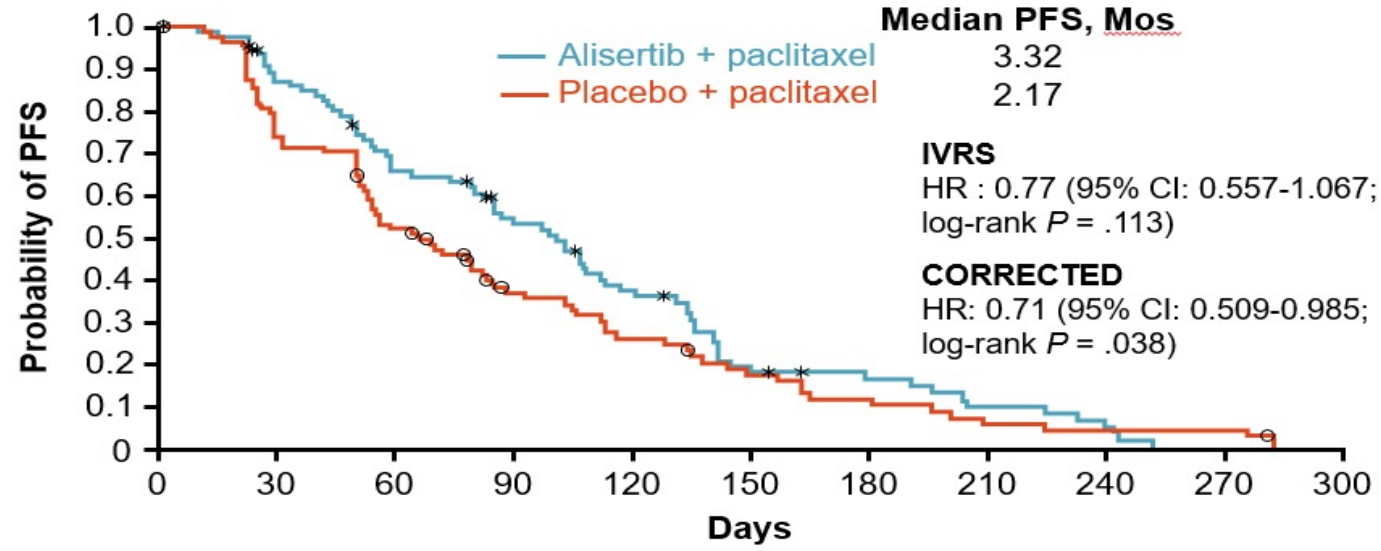
ATR inhibitor (M6620) – Study Design and ORR



Cancer Cell. 2021;39(4):566-579.

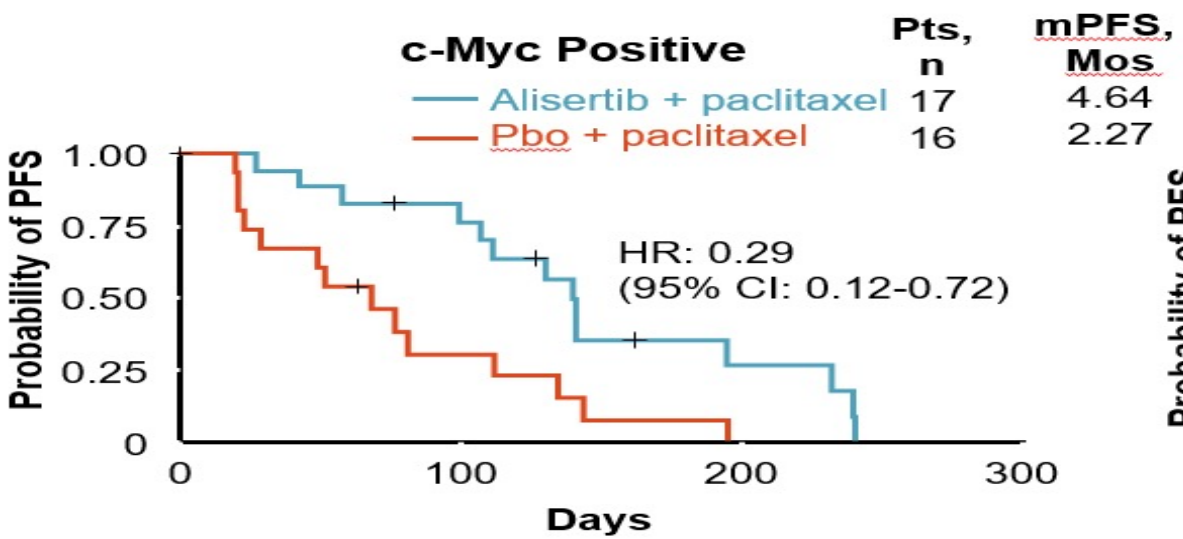
Relapsed SCLC

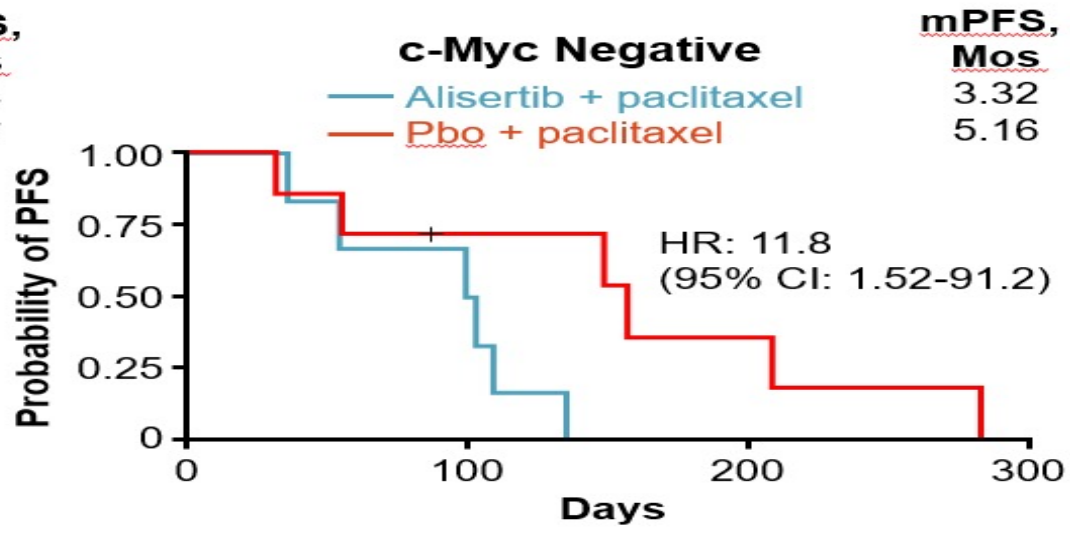
Alisertib + Paclitaxel vs Paclitaxel - PFS (ITT) and by c-Myc Expression



Archived tumor tissue available for 44 pts;
c-Myc +ive vs c-Myc –ive:
P_{binary} = .0006

Owonikoko TK, et al. WCLC 2016. Abstract OA05.05.

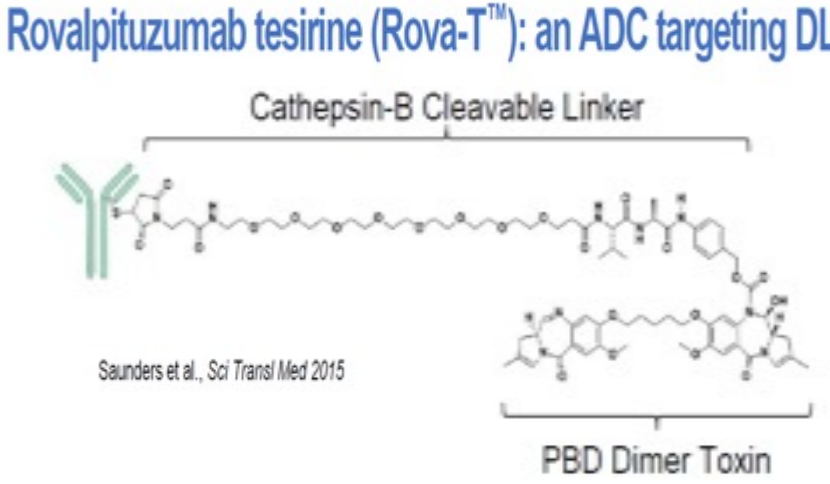


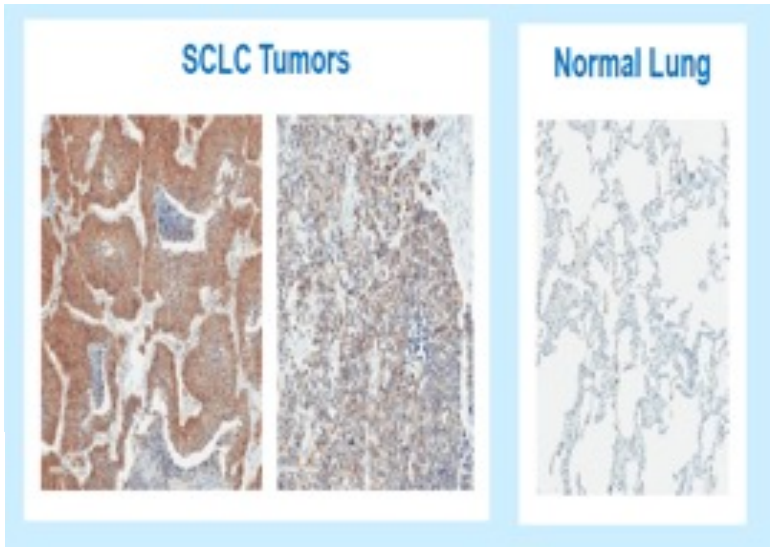


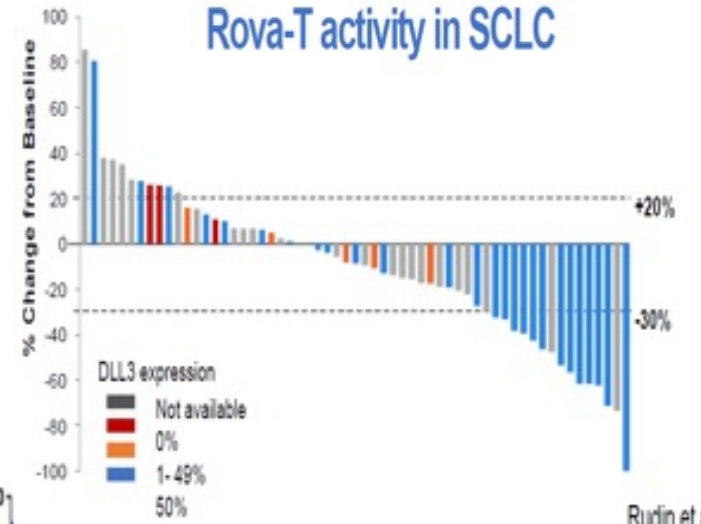
DLL3 - NOTCH Ligand

Antibody Drug Conjugate (ADC): Rova-T

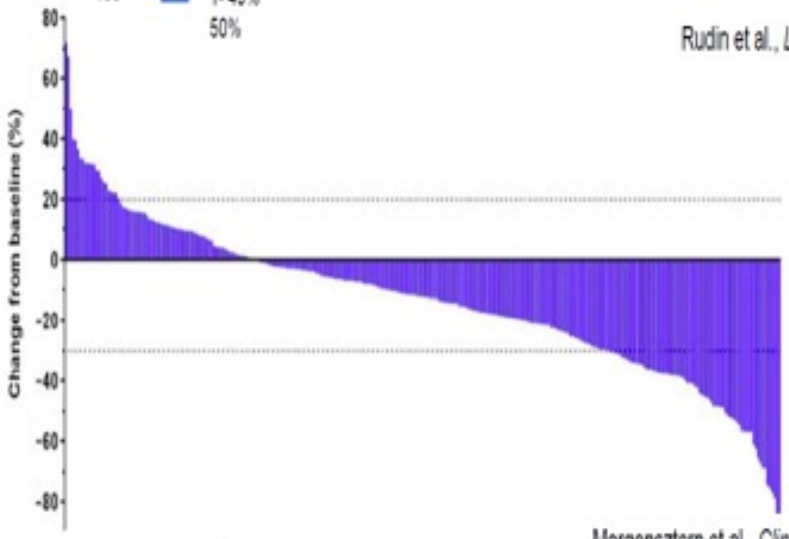
DELTA-LIKE LIGAND 3 (DLL3) IS A HIGHLY SPECIFIC TARGET IN SCLC







Rudin et al., *Lancet Oncol* 2017

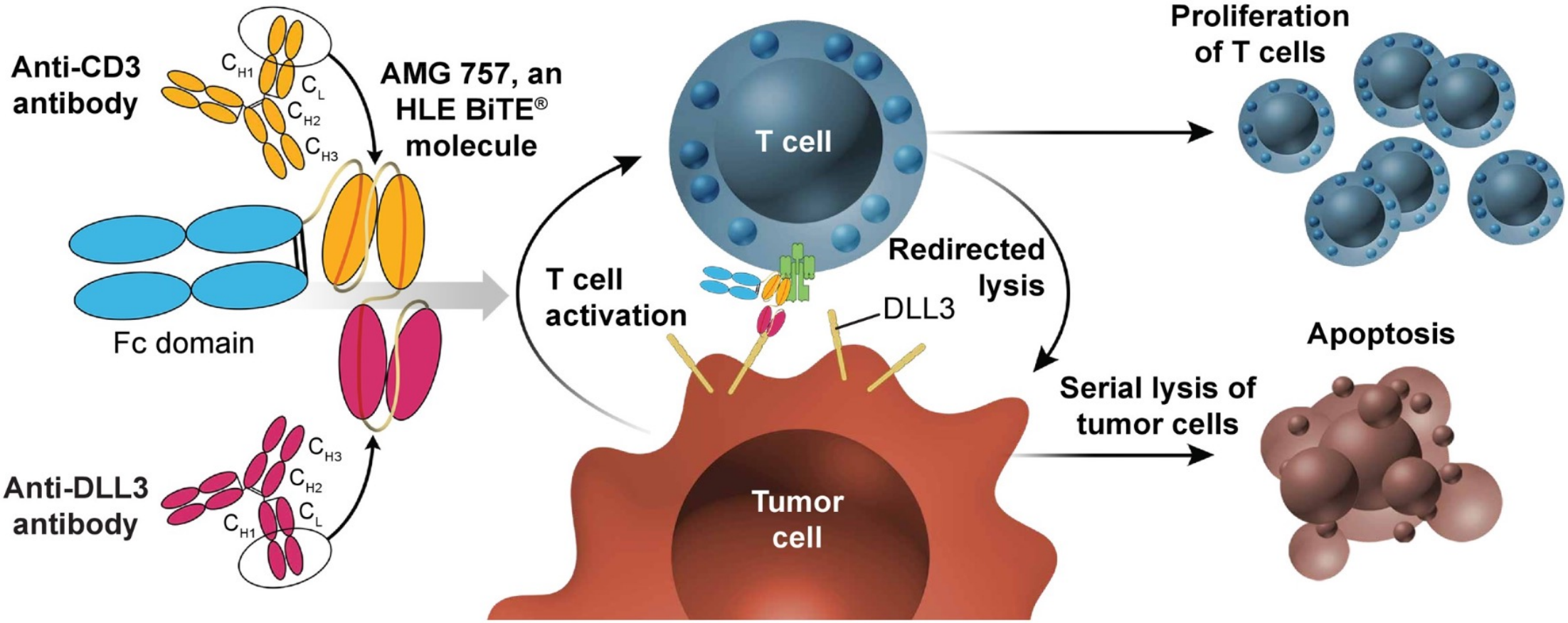


Morgensztern et al., *Clin Cancer Res* 2019

AMG 757

Half-life Extended DLL3-Directed Bispecific Antibody (BiTE)

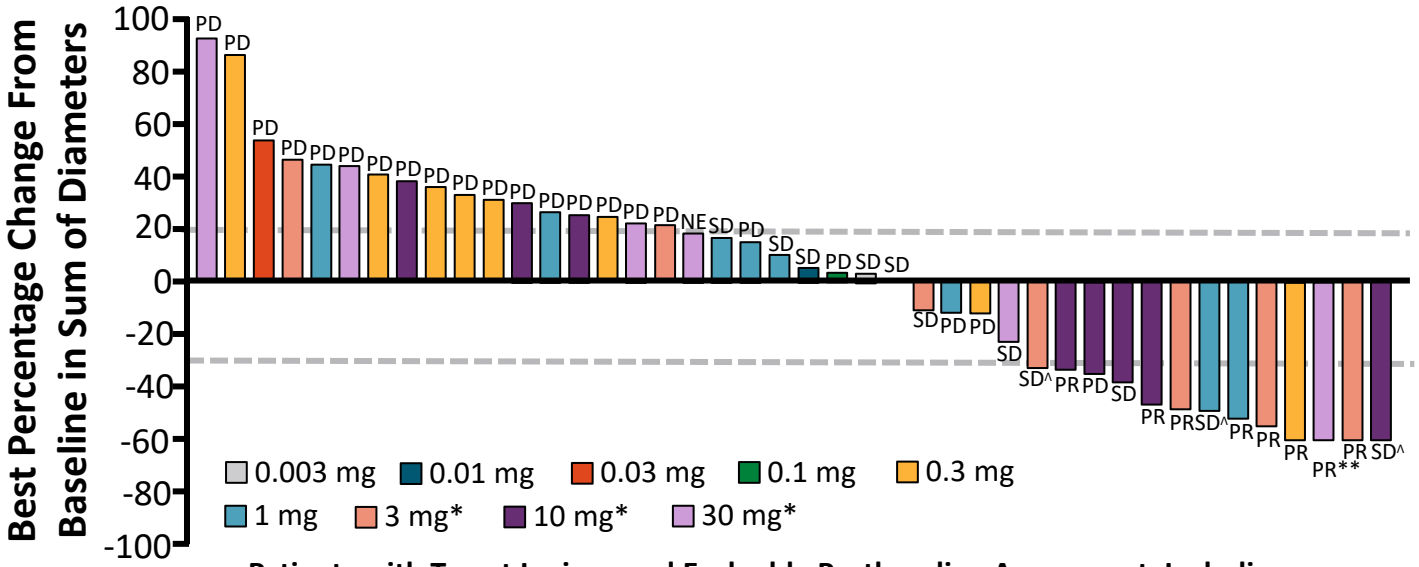
Figure 2. AMG 757 Is a Half-life Extended BiTE® Immuno-oncology Therapy



C_H, heavy chain constant domain; C_L, light chain constant domain; HLE BiTE®, half-life extended bispecific T-cell engager; CD, cluster of differentiation; DLL3, delta-like ligand 3; Fc, crystallizable fragment.

AMG 757 in Relapsed SCLC

Antitumor Activity



Patients with Target Lesions and Evaluable Postbaseline Assessment, Including Sum of Diameters (n = 42)

Response per mRECIST v1.1	Patients (n = 51†)
Confirmed PR, n (%)	7 (14)
Confirmed PR by target dose, n/N (%)	
▪ 0.3 mg	1/12 (8)
▪ 1.0 mg	1/8 (13)
▪ 3.0 mg	3/9 (33)
▪ 10.0 mg	2/10 (20)
Unconfirmed PR, n (%)	1 (2)‡
SD, n (%)	11 (22)
DCR, %	37

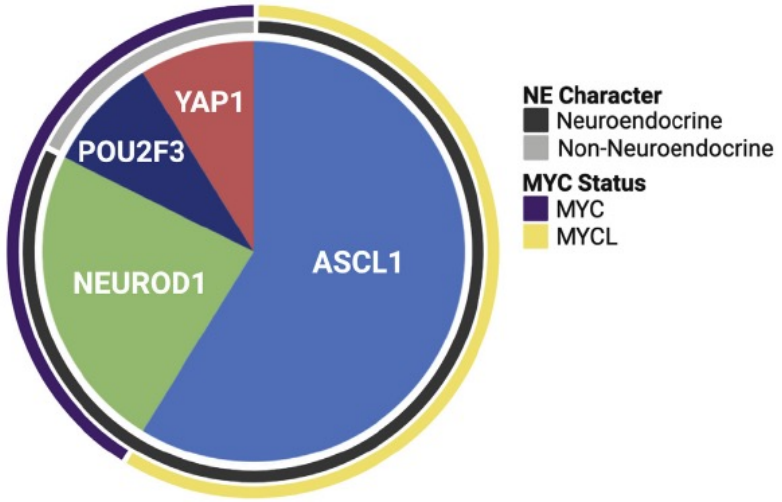
PR**, unconfirmed PR; SD^, initial PR not confirmed on subsequent scan; NE, PD in post-baseline scan and went off study without confirmation scan. *Step dosing.
†Includes those treated with ≥ 1 dose of AMG 757 and with follow-up ≥ 8 wks.
‡At target dose of 30 mg.

- Antitumor activity observed with AMG 757 during dose exploration

Owonikoko. WCLC 2020. Abstr OA11.03. Reproduced with permission.

Molecular subtypes of SCLC

Potential Therapeutic Implications



	ASCL1	NEUROD1	POU2F3	YAP1
Targeted Therapies	BCL2 CREBBP DLL3 LSD1	Arginine Deprivation AURKA/B CHK1 IMPDH LSD1	Arginine Deprivation AURKA/B CHK1 IGF-R1 IMPDH	Arginine Deprivation AURKA/B CHK1 IMPDH IO

Figure 3. Diagram of the relative abundance, MYC status, and NE character of the four molecular subtypes of SCLC, each identified by their key transcriptional regulator. These subtypes may exhibit distinct targetable vulnerabilities, which are represented in the table beneath the pie chart. Proportions of each subtype are as follows: ASCL1 (0.70, 95% CI: 0.60-0.79), NEUROD1 (0.11, 95% CI: 0.06-0.20), YAP1 (0.02, 95% CI: 0.01-0.09), POU2F3 (0.16, 95% CI: 0.10-0.26). ASCL1, achaete-scute homolog 1; AURKA/B, Aurora kinase A/B; BCL2, B-cell lymphoma 2; CREBBP, CREB-binding protein; CHK1, checkpoint kinase 1; DLL3, delta-like ligand 3; IMPDH, inosine-5' monophosphate dehydrogenase; IGF-R1, insulin-like growth factor 1 receptor; IO, immuno-oncology; LSD1, lysine-specific histone demethylase 1; NE, neuroendocrine; NEUROD1, neurogenic differentiation factor 1; POU2F3, POU class 2 homeobox 3; YAP1, yes-associated protein 1.

Data on molecular heterogeneity of SCLC holds promise for biomarker driven personalized therapeutic approaches

Preclinical studies suggest distinct therapeutic vulnerabilities in the novel marker-defined subtypes of SCLC

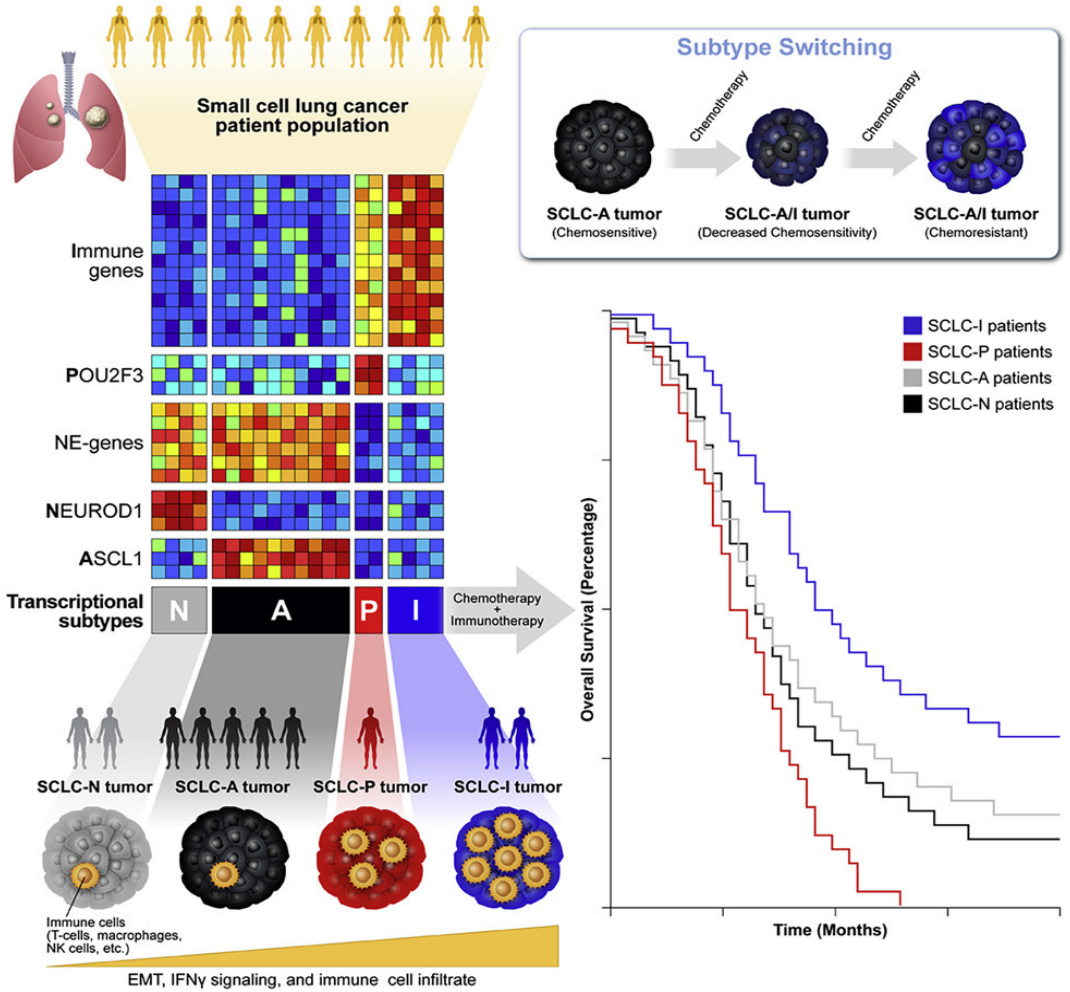
Clinical studies

- Retrospective
- Not prospective yet

JTO 2020; 15(4):520-540

Molecular subtypes of SCLC

Potential Biomarkers Implications



- Four subtypes with unique molecular features and therapeutic vulnerabilities
  - Differential expression of ASCL1, NEUROD1, and POU2F3 defines SCLC subtypes
  - An inflamed, mesenchymal, subtype (SCLC-I) has low expression of ASCL1, NEUROD1, and POU2F3
- SCLC-I experiences greatest benefit from the addition of anti-PD-L1 to chemotherapy
- Subtypes with specific genomic alterations
  - All subtypes with similar mutational landscape (including TP53 and RB1)
- Phenotype (genomic, transcriptomic, proteomic)
  - SCLC-A: highly NE, epithelial, TTF-1+
  - SCLC-N: highly NE, largely TTF-1-
  - SCLC-P: non-NE, low EMT
  - SCLC-I: non-NE, high EMT
- Intratumoral subtype switching accompanies acquired resistance to platinum chemotherapy

Gay et al. Cancer Cell 2021; 39:346–360

Notch Signaling in SCLC

Determinant of response to ICI

Notch signaling and efficacy of PD-1/PD-L1 blockade in relapsed small cell lung cancer

- Immunogenomic profiling of relapsed SCLC tumors treated with Immune Checkpoint Blockade (ICB).
- Tumors deriving clinical benefit from ICB exhibited cytotoxic T-cell infiltration, high expression of antigen processing and presentation machinery (APM) genes, and low neuroendocrine (NE) differentiation.
- Notch signaling, (correlates positively with low NE differentiation), most significantly predicts clinical benefit to ICB.
- Activation of Notch signaling (overexpression of NOTCH1 intracellular domain) in a (high) NE human SCLC cell line induces transition to a low NE phenotype
  - marked by increased expression/upregulation of APM genes
- Mechanistic link between Notch activation, low NE differentiation and increased intrinsic tumor immunity.

Roper, et al. Nat Commun. 2021 Jun 23;12(1):3880.

Table 2 Notch signaling gene set is the most significant predictor of clinical benefit to immune checkpoint blockade across relapsed SCLC cohorts.

Variable	Estimate[a]	*t* value[a]	*p* value[a]	FDR[b]
Hallmark Notch signaling	0.25	4.31	9.8×10^{-4}	5.9×10^{-4}
Immune signature	0.13	2.06	0.047	0.14
NE score	−0.07	−1.82	0.08	0.16
MYC expression	−0.04	−0.83	0.41	0.62
EZH2 expression	−0.03	−0.56	0.58	0.62

Outcome dependent variable = clinical benefit to immune checkpoint blockade.
[a]Estimates, *t* and *p* values calculated using multivariable logistic regression.
[b]False discovery rate was calculated using the Benjamini–Hochberg procedure.

Table 1 Association between transcriptional subtypes and clinical benefit to immune checkpoint blockade across relapsed SCLC cohorts.

Transcriptional subtype	Clinical benefit (# of tumors)	No clinical benefit (# of tumors)	*p* value[a]
ASCL1	2	22	0.11
NEUROD1	3	9	0.40
POU2F3	1	0	0.17
YAP1	2	8	0.78

[a]Statistical significance calculated using the two-tailed chi-squared test.