Small cell lung cancer

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Outline

- Small cell lung cancer 101
- Genetic abnormalities of small cell lung cancer
- SCLC conversion as a resistance mechanism to EGFR TKI in lung adenocarcinoma
- Examples of translational medicine: Story of Rova-T
- Examples of translational medicine: Immune checkpoint inhibitors
- Extrapulmonary small cell carcinoma

Morphology of SCLC

Small cell lung cancer (SCLC) is also known as oat cell carcinoma. Its morphology resembles oat grains and appears as small oval cells with scanty cytoplasm.

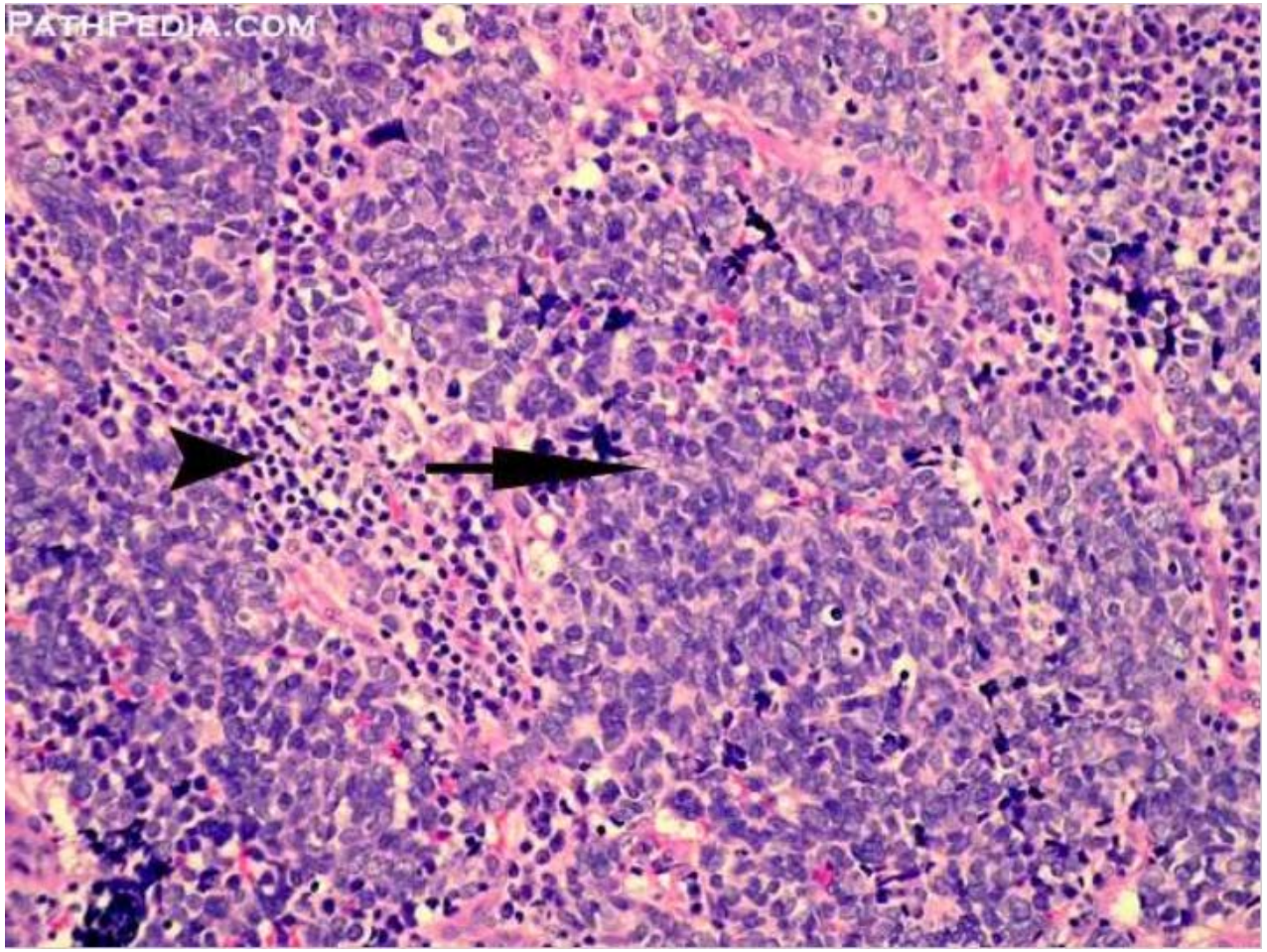


Image obtained from Pathpedia.com

SCLC 101

- Lung cancer is conventionally divided into small-cell lung cancer (SCLC) and non-small cell lung caner (NSCLC).
- SCLC accounts for 10% to 15% of all lung cancer cases, and is closely linked to the intensity and duration of tobacco smoking.
- Compared to NSCLC, SCLC tends to disseminate earlier in the course of its natural history and displays a more aggressive clinical behavior.
- SCLC is also commonly associated with paraneoplastic endocrinopathies, such as Cushing syndrome and Lambert-Eaton myasthenic syndrome.

SCLC is a recalcitrant cancer

- Recalcitrant cancer:
  - Have a 5-year relative survival rate of less than 20%
  - Estimated to cause the death of at least 30,000 individuals in the United States per year.
- NCI identified four major obstacles to progress in 2014:
  - Continuing risk of developing the disease that remains for decades after smoking cessation.
  - Most patients have widely metastatic tumors at the time of diagnosis.
  - Rapid development of resistance to chemotherapy in more than 95% of SCLC patients.
  - Lack of tumor tissue for clinical, molecular, and cell biological studies.

SCLC:

<7%

~30,000 deaths/yr

Staging of SCLC: 2-stage system

- Limited disease-SCLC (30-40%)
  - Definition: Tumor and nodes confined to one hemithorax and able to be encompassed within a single radiotherapy port
  - Treatment: Combination chemotherapy with thoracic radiation
  - Median Overall survival: 15-20 months

- Extensive disease-SCLC:
  - Definition: All others.
  - Treatment: Combinatory chemotherapy
  - Median Overall survival: 8-13 months

Systemic therapy of SCLC

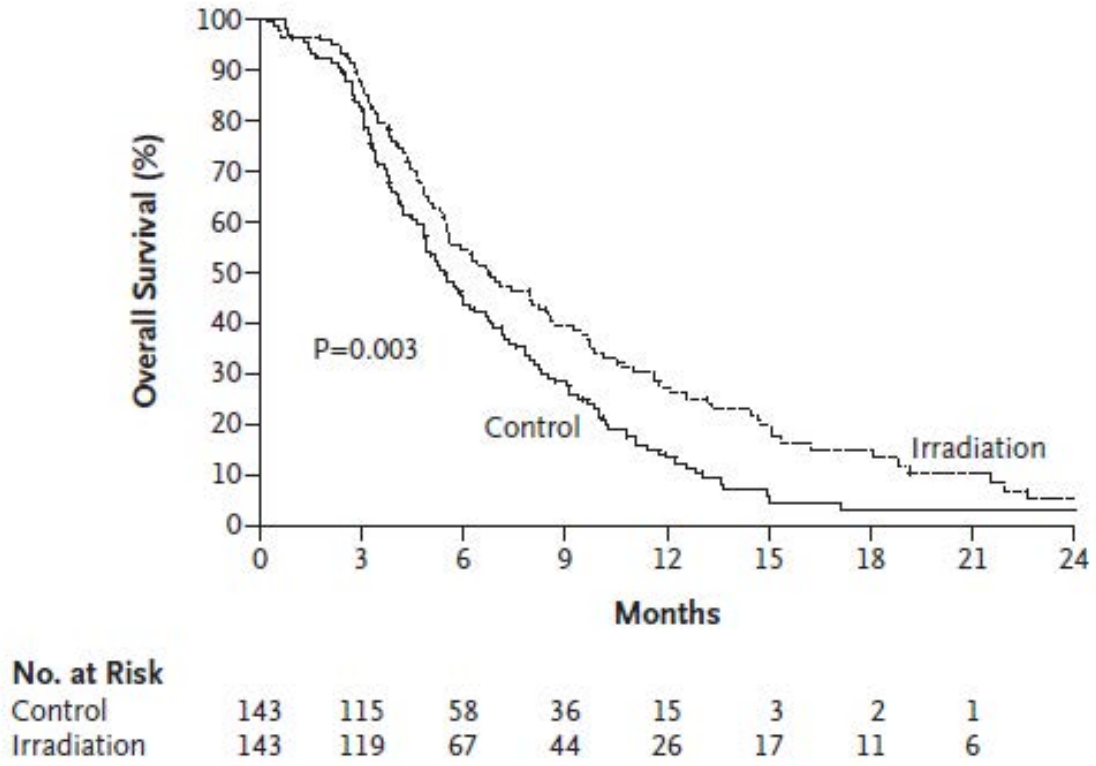
- It was learned quite early in the 1970s that combinatory therapy produces superior survival compared with single-agent treatment based on several randomized trials.
- First-line therapy: platinum + etoposide
  - Sensitive disease: relapse after three months of the last day of initial treatment
  - Refractory disease: relapse within three months of the last day of initial treatment
- Second-line therapy: topotecan
- Third-line therapy: nivolumab

PCI (prophylactic cranial irradiation)

1. SCLC commonly metastasizes to brain.

2. In 1990s, meta-analysis shows that PCI improves overall survival in SCLC patients with complete remission from initial therapy.

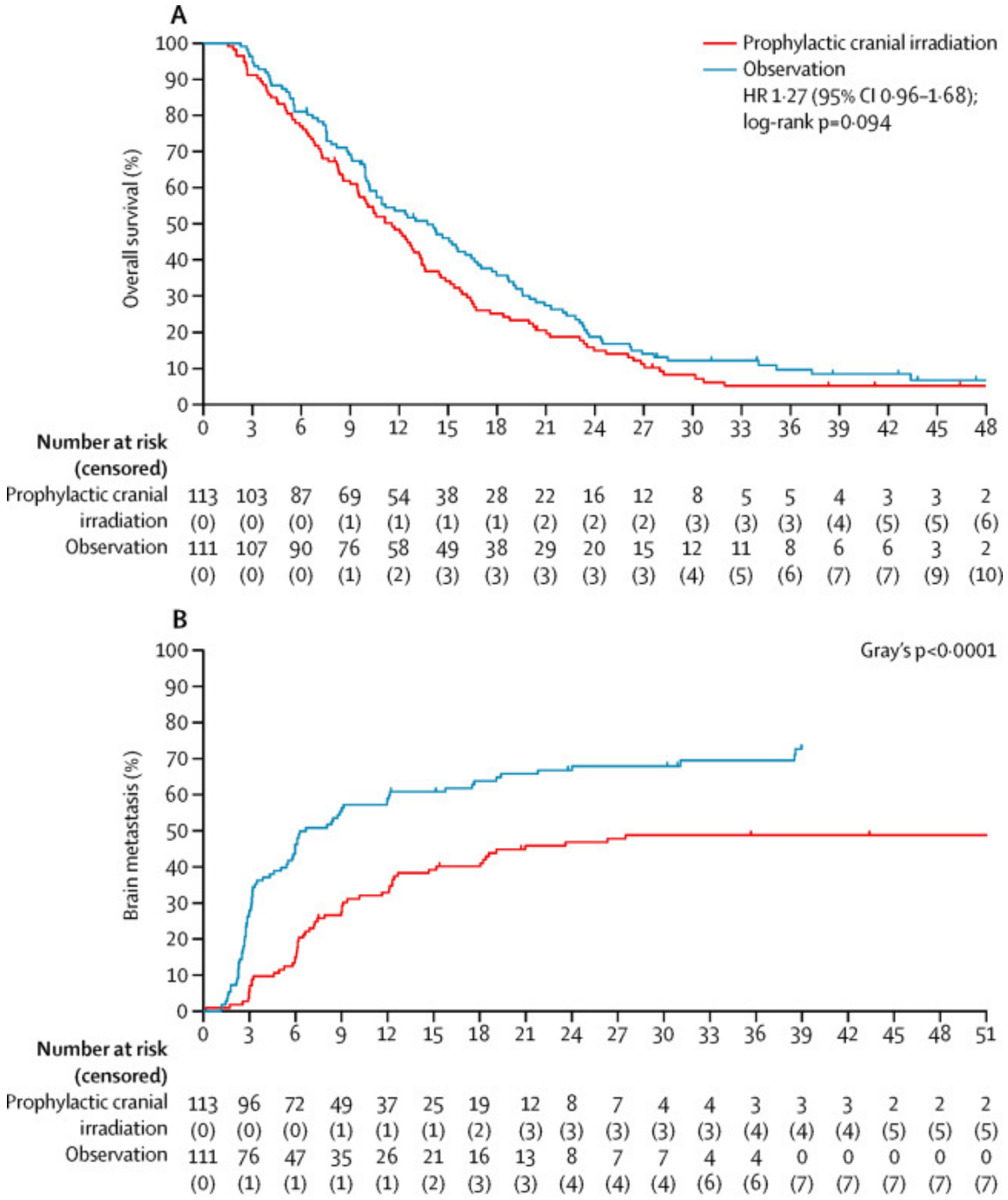
3. In 2007, PCI was proved to decrease brain metastasis, and improve PFS and OS in extensive-disease SCLC patients with a response after initial chemotherapy.



Slotman et al. NEJM 2007;357:664-672

PCI (cont.)

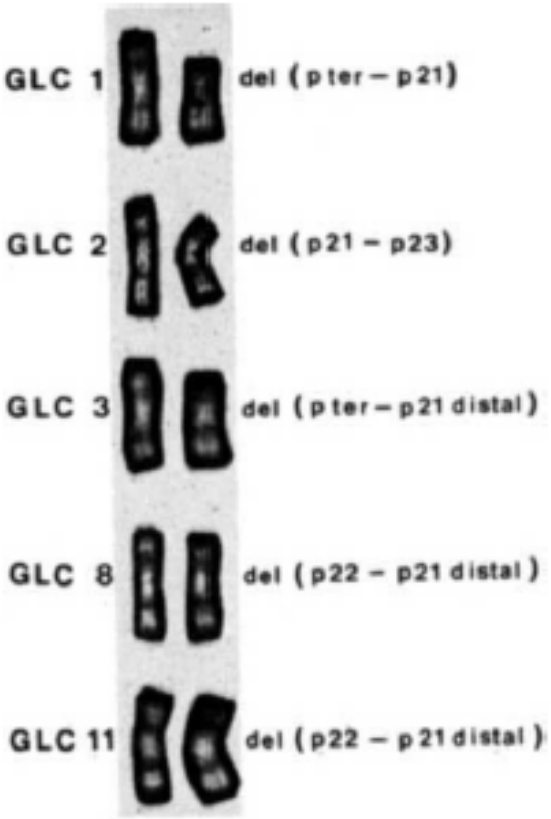
In a recent Japanese trial, PCI did not result in longer overall survival compared with observation in patients with extensive-disease small-cell lung cancer, who had any response to platinum-based doublet chemotherapy and no brain metastases on MRI.



Takahashi, et al. Lancet Oncology 18 (5), p663–671

Genetic abnormalities of SCLC

Genetic abnormalities of SCLC– Deletion of 3p21



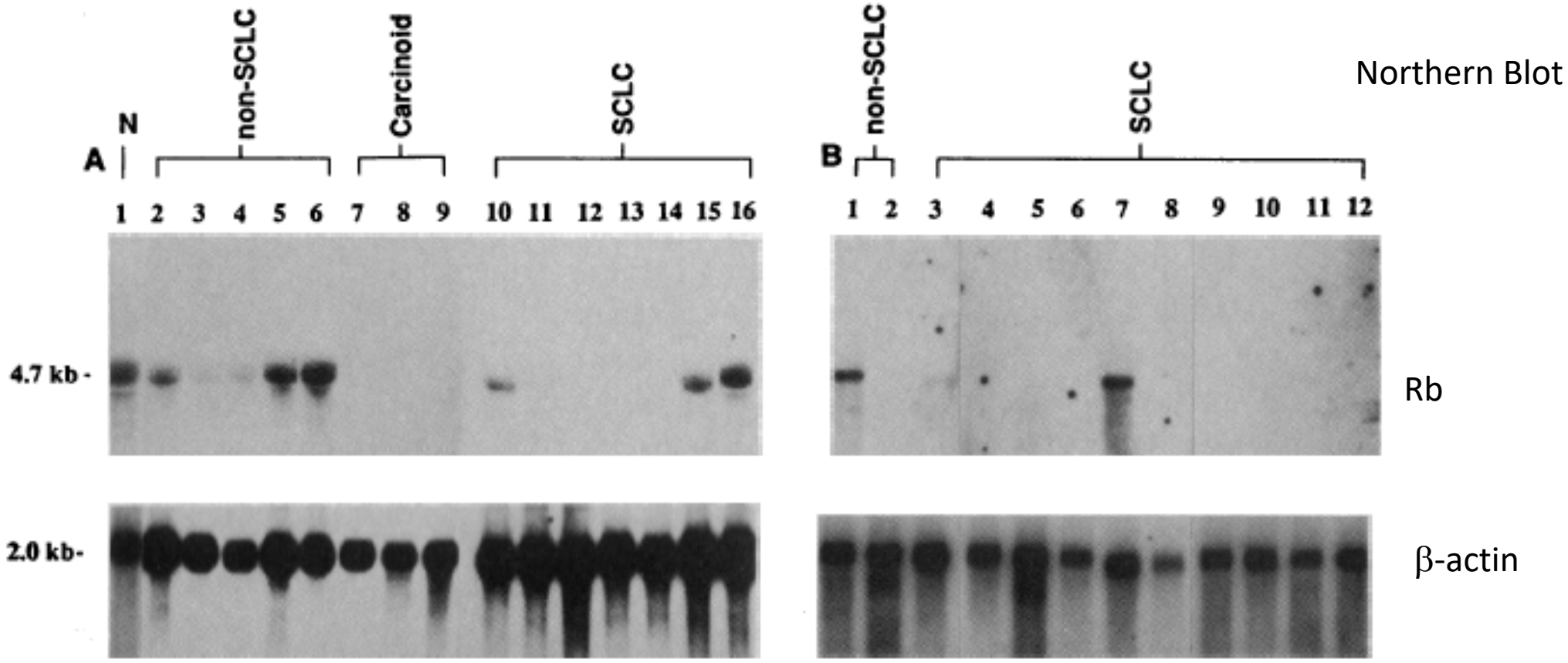
- Chromosomal region 3p21 was found to be consistently deleted not only in SCLC (almost 100%), but in all major types of lung cancer (more than 90%).

- Chromosome 3p abnormalities appear early in the pathogenesis of lung cancer and are found as clonal lesions in the smoking damaged respiratory epithelium including histologically normal epithelium as well as in epithelium showing histologic changes of preneoplasia.

Kok et al. Nature 1987,**330:**578-581

Genetic abnormalities of SCLC– Loss of Rb gene

- Besides chromosome 3p deletion, chromosomal regions of 13q and 17p are also frequently affected in SCLC.



Harbour W et al. Science. 1988, 241:353-7.

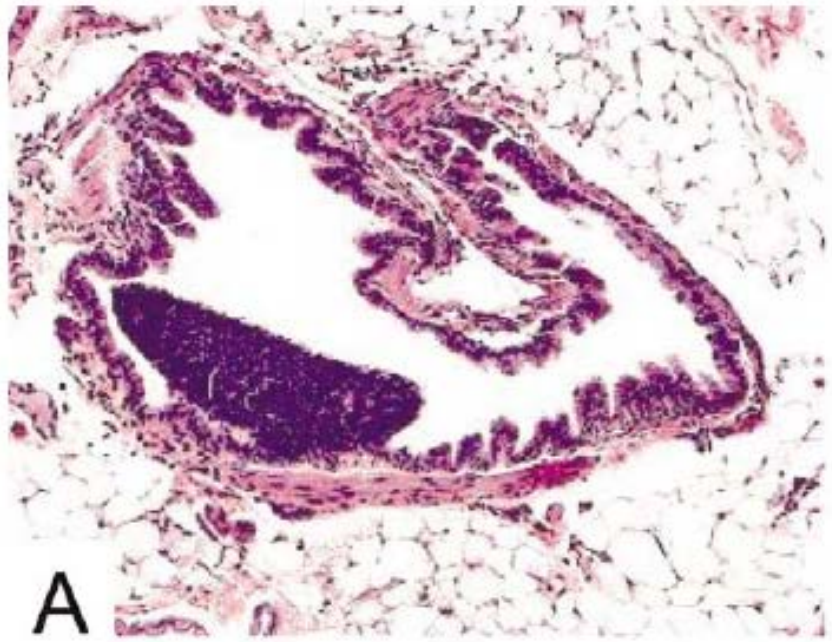
Genetic abnormalities of SCLC – Inactivation of TP53 gene

Table 1. Abnormalities of p53 in lung cancer lines. Terms and symbols for mRNA levels are as follows: +, easily detectable p53 transcripts comparable to levels found in normal lung; reduced or trace, greatly reduced amount of transcript compared to normal lung; undetectable, undetectable by both Northern blot analysis and the RNase protection assay. Full designation of the cell lines includes the prefix "NCI". All but H60, H69, H82, H187, H345, H378, and H510 were established from patients before treatment.

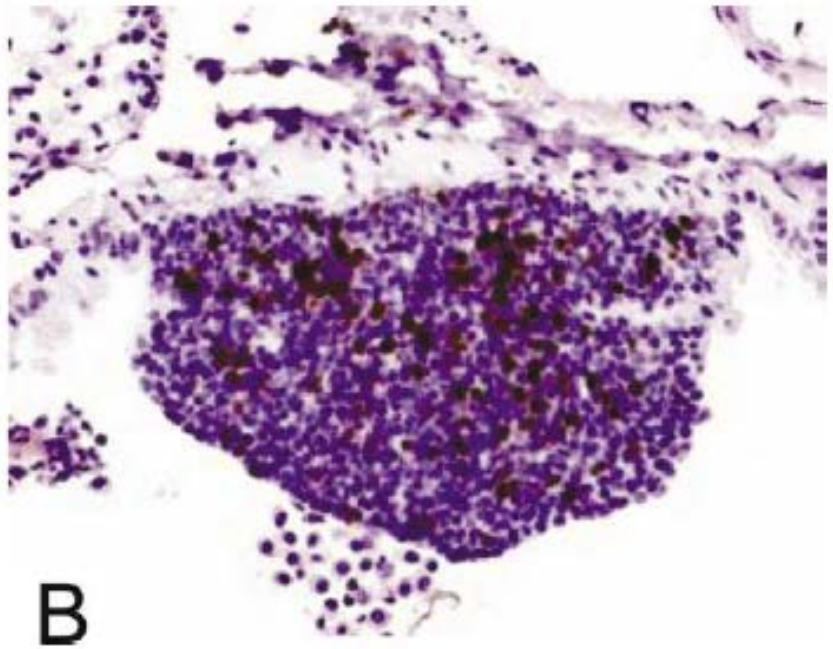
Type of mutations	mRNA level	Tumor cell type	Cell line
Homozygous deletion	Undetectable	Bronchioloalveolar	H358
Homozygous deletion with truncated mRNA	Reduced	Extrapulmonary small cell	H660
DNA rearrangement	Undetectable	Adenocarcinoma	H969
Abnormal size mRNA	+	Small cell	H526
	+	Adenocarcinoma	H676
	+	Adenosquamous	H647
	Trace	Small cell	H82
Point or small mutation	+	Small cell	H1436, H1450
	+	Pulmonary carcinoid	H727
	+	Adenocarcinoma	H23
	+	Bronchioloalveolar	H820
	+	Adenosquamous	H125
	+	Large cell	H661
	Reduced	Small cell	H889, H1092
	Reduced	Adenocarcinoma	H920
None detected	Trace	Small cell	H60, H69, H209, N417
	Reduced	Squamous	H520
None detected	+	Small cell	H187, H345, H378
	+	Extrapulmonary small cell	H510
	+	Adenosquamous	H596
	+	Squamous	H226
	+	Large cell	H460, H1385

Takahashi et al. Science 1989, 246:491-4

Conditional inactivation of Trp53 and Rb1 led to SCLC in mouse models



Hyperplastic focus in the airway
(H&E staining)



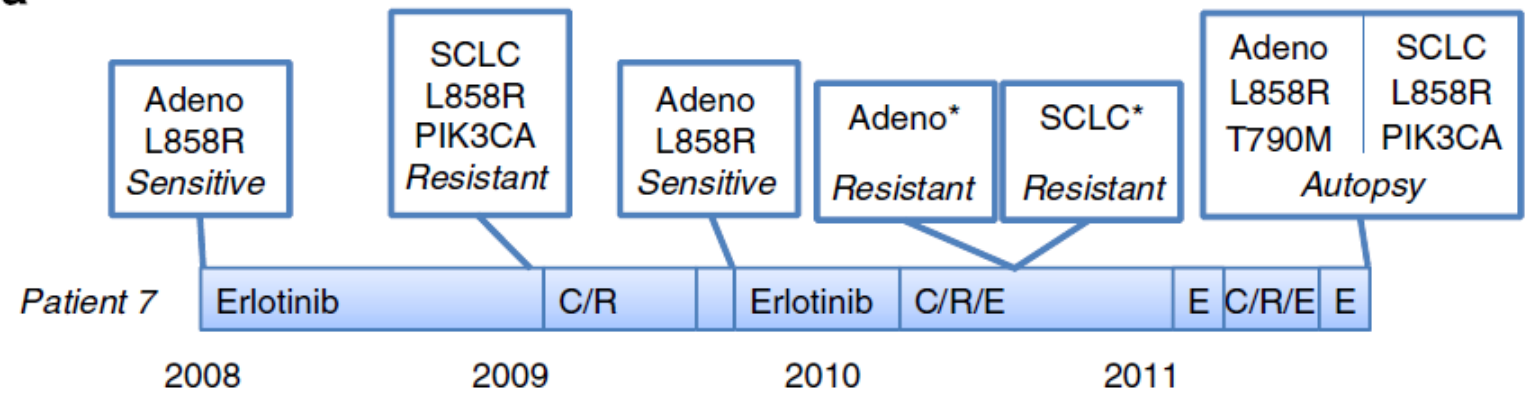
Anti-BrdU staining

SCLC became detectable within 196-350 days in the mouse model with conditional inactivation of TP53 and Rb1.

Meuwissen R et al. Cancer Cell. 2003, 4: 181-9

SCLC conversion is a resistance mechanism to EGFR TKI in lung adenocarcinoma

a



b

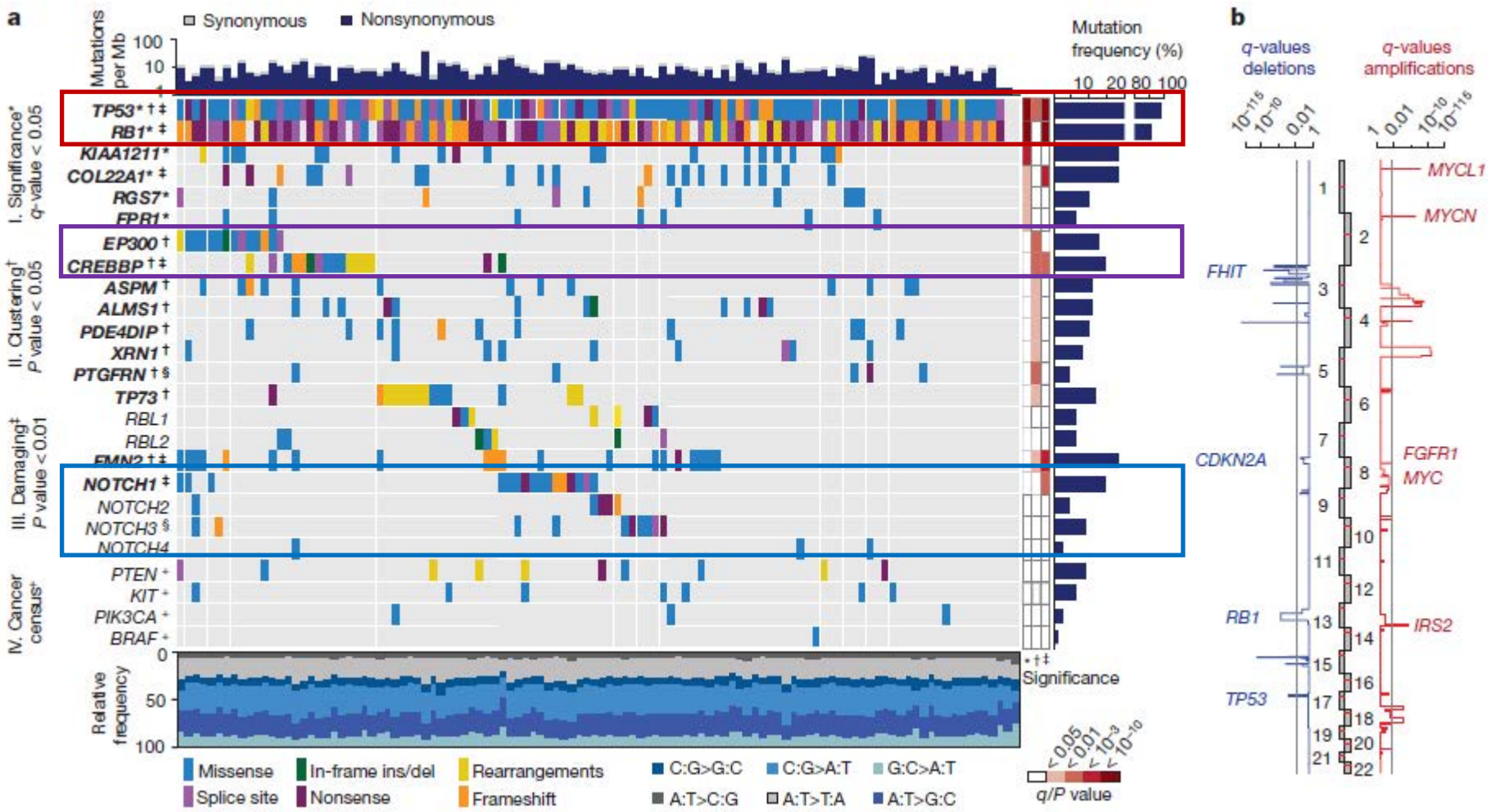
Sample	Normal liver	Diaphragm tumour	Lung tumour	Liver tumour
Histological features	Normal tissue	Adenocarcinoma	SCLC	SCLC
Number of reads	179,298,190	350,864,233	388,189,232	318,482,313
Average coverage	146	287	319	253
Primary *EGFR* mutation	WT	L858R	L858R	L858R
Secondary *EGFR* mutation	WT	T790M	WT	WT
PIK3CA status	WT	WT	E545K	E545K
TP53 status	WT	WT/Δ154–163	–/Δ154–163	–/Δ154–163

Table 1 | RB status of TKI-resistant patients.

Patient	Cancer type	Resistance	Histology	RB status	Detection method
1	Lung	Pre	Adeno	Pos	IHC
	Lung	Post	NE	Neg	IHC/genetic
	Lung	Post	NE	Neg	IHC/genetic
2	Lung	Pre	Adeno	Pos	IHC
	Lung	Pre	Adeno	Neg	IHC
	Lung	Post	NE	Neg	IHC
3	Lung	Pre	Adeno	Pos	IHC
	Lung	Post	NE	Neg	IHC
4	Lung	Post	NE	Neg	IHC
5	Lung	Post	NE	Neg	IHC
6	Lung	Pre	Adeno	Neg	IHC
	Lung	Post	NE	Neg	IHC/genetic*
7	Lung	Post	Adeno	Pos	IHC/genetic
	Lung	Post	NE	Neg	IHC/genetic
	Lung	Post	NE	Neg	Genetic
8	Lung	Post	Adeno	Pos	IHC
	Lung	Post	NE	Neg	IHC
9	Lung	Post	NE	Neg	IHC
10	Lung	Post	Adeno	Neg	IHC
11	Lung	Pre	Adeno	Pos	IHC
	Lung	Post	Adeno	Pos	IHC
12	Lung	Pre	Adeno	Pos	IHC
	Lung	Post	Adeno	Pos	IHC
13	Lung	Post	Adeno	Pos	IHC
14	Lung	Pre	Adeno	Pos	IHC
	Lung	Post	Adeno	Pos	IHC
15	Lung	Post	Adeno	Pos	IHC
16	Lung	Pre	Adeno	Pos	IHC
	Lung	Post	Adeno	Pos	IHC
17	Lung	Pre	Adeno	Pos	IHC
	Lung	Post	Adeno	Pos	IHC
18	Lung	Post	Adeno	Pos	IHC
19†	Lung	Intrinsic	NE	Neg	IHC

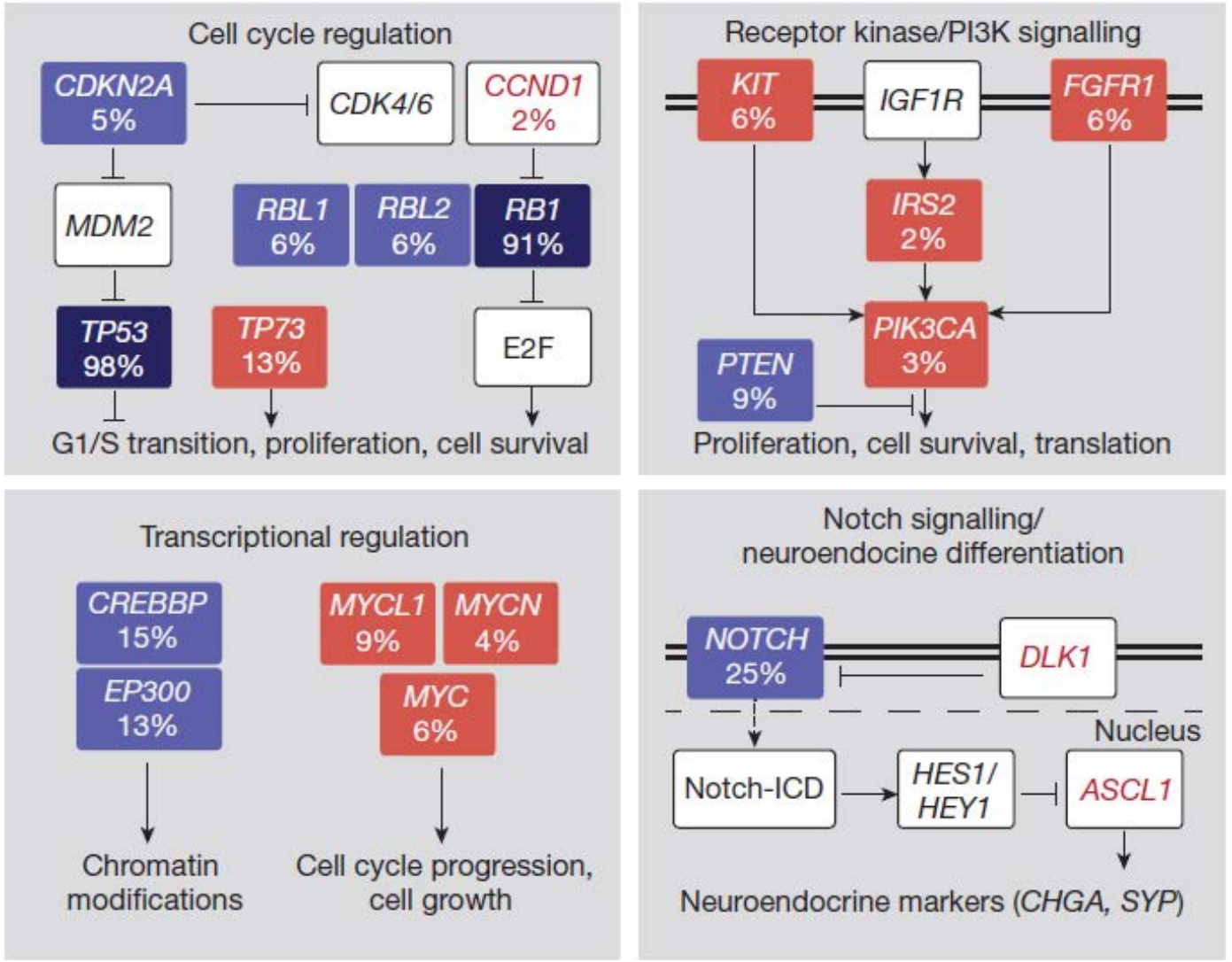
Niederst MJ et al. Nat Commun. 2015;6:6377.

Genomic abnormalities of SCLC: WES Analysis



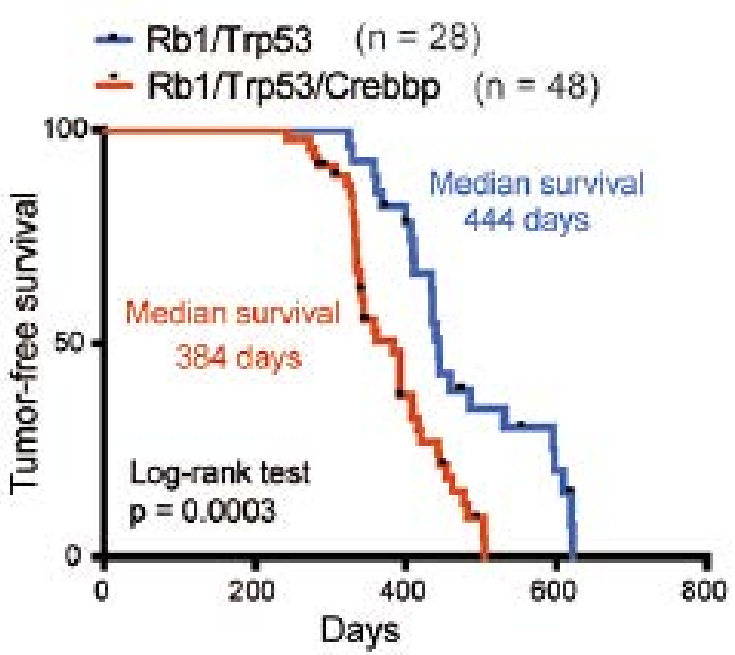
George et al. Nature 2015;524(7563):47-53

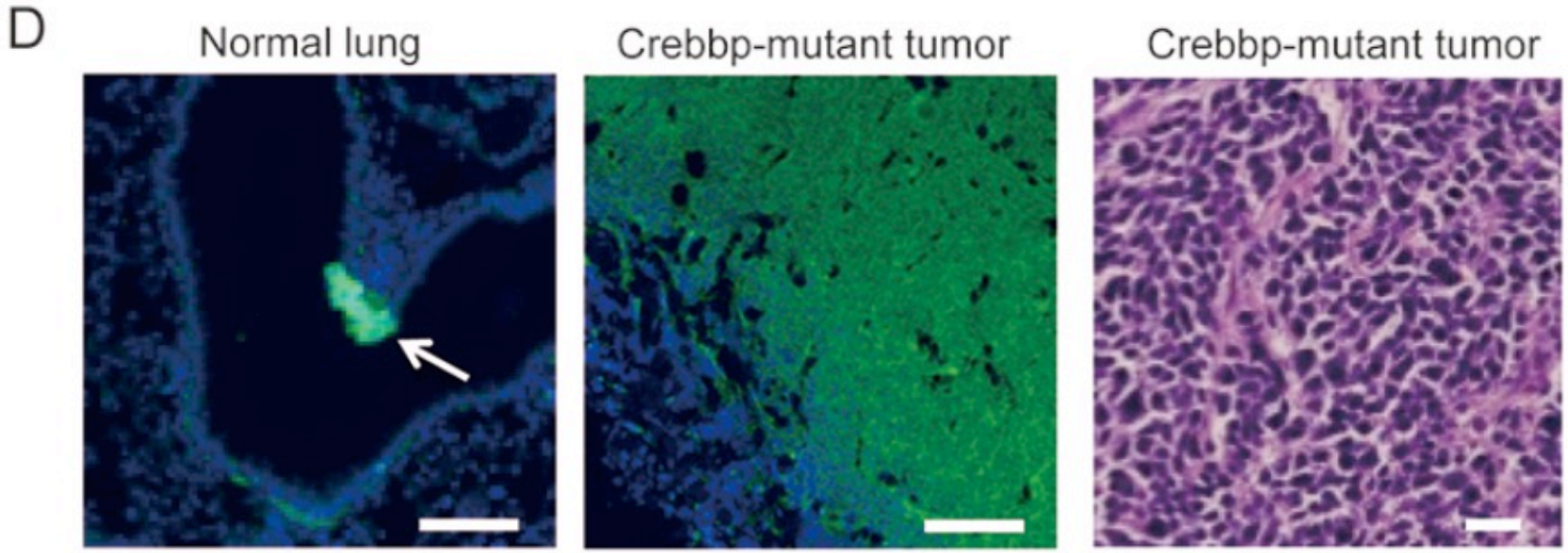
Pathways that are recurrently affected in SCLC



George et al. Nature 2015;524(7563):47-53

Inactivation of Crebbp accelerated development of SCLC in a mouse model

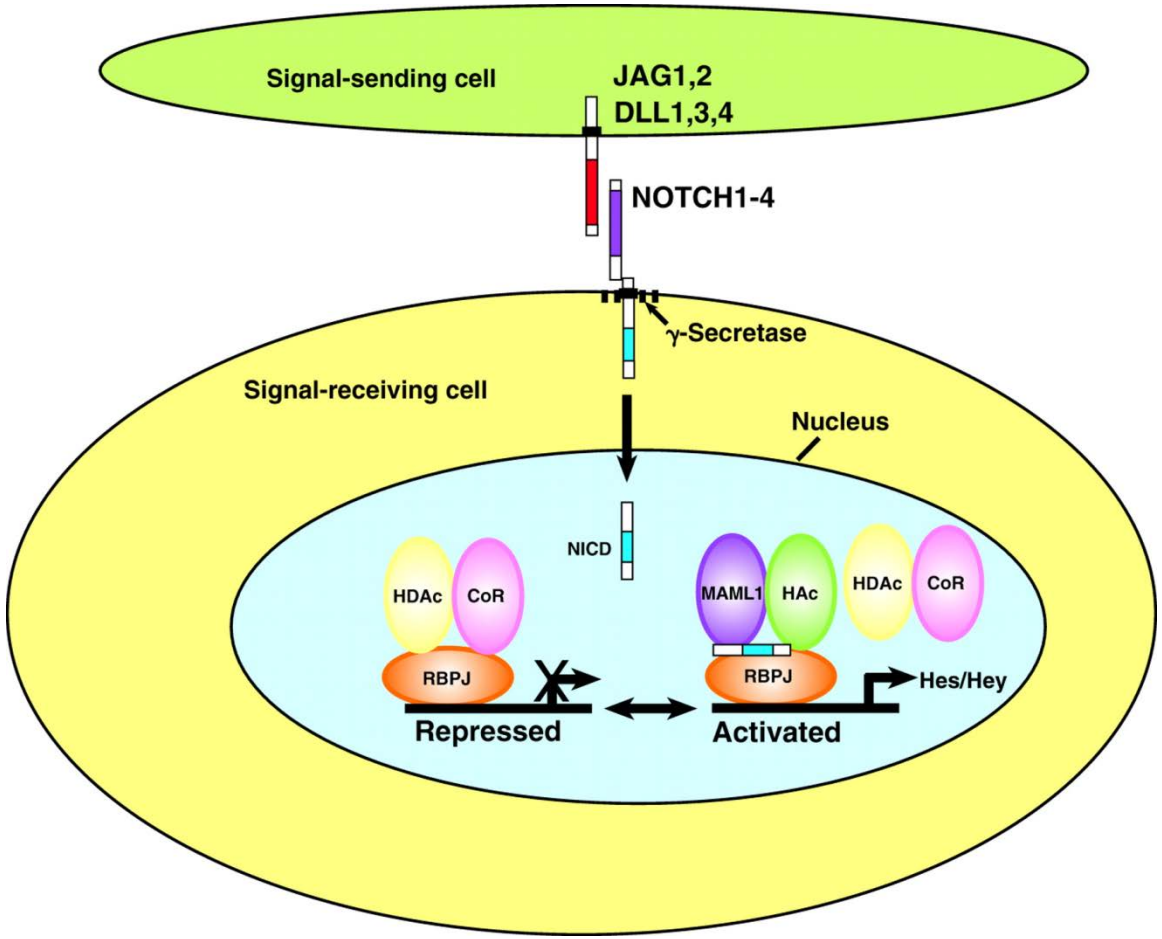




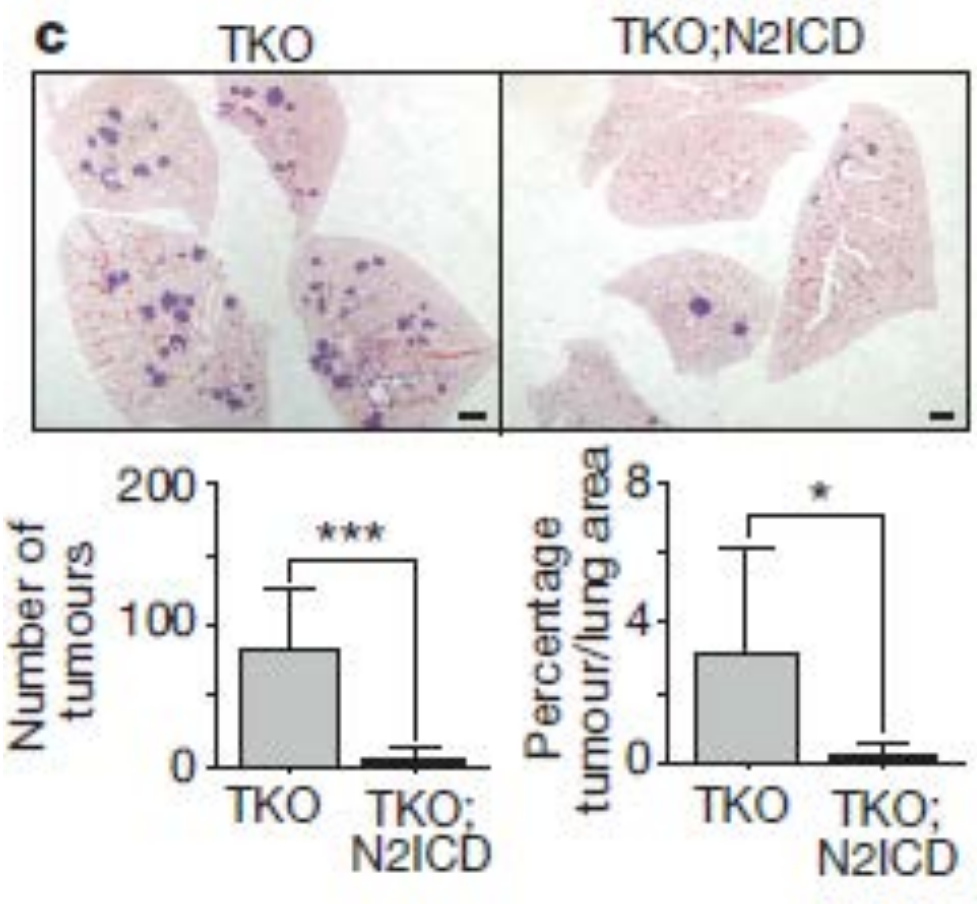
Jia et al. Cancer Discovery, 2018

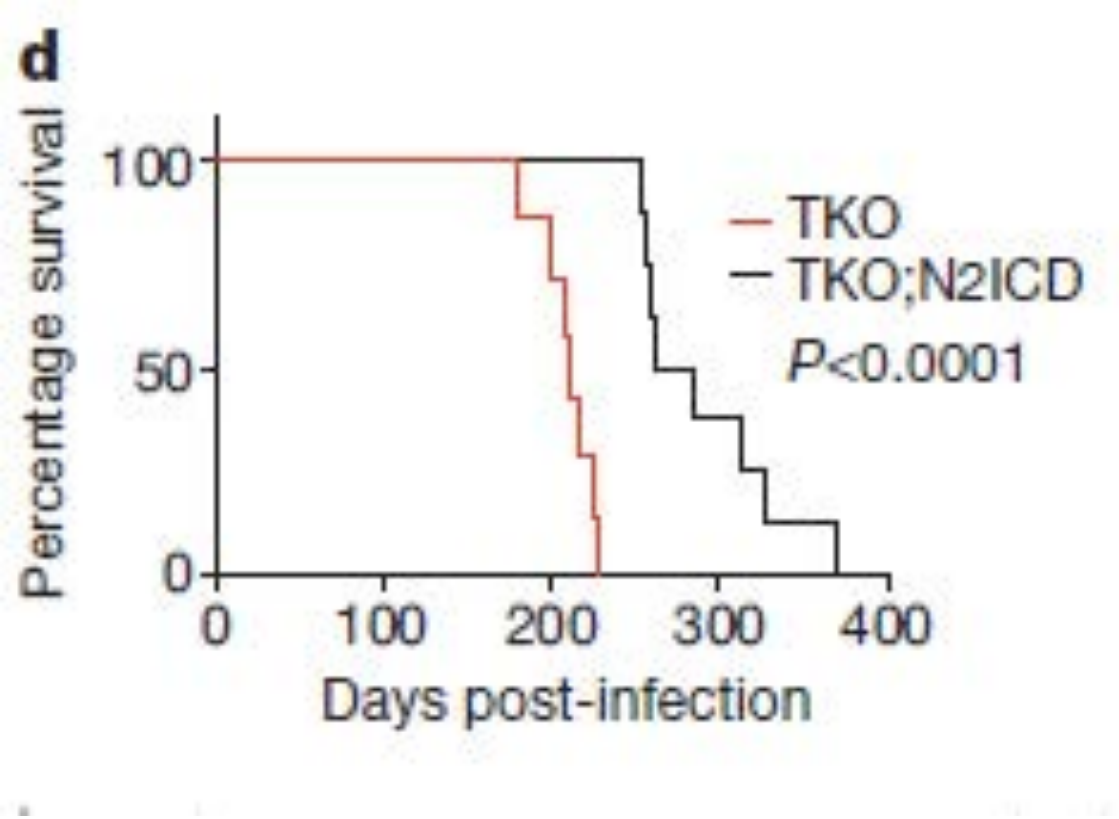
Examples of Translational medicine: Story of Rova-T

Notch Signaling Pathway



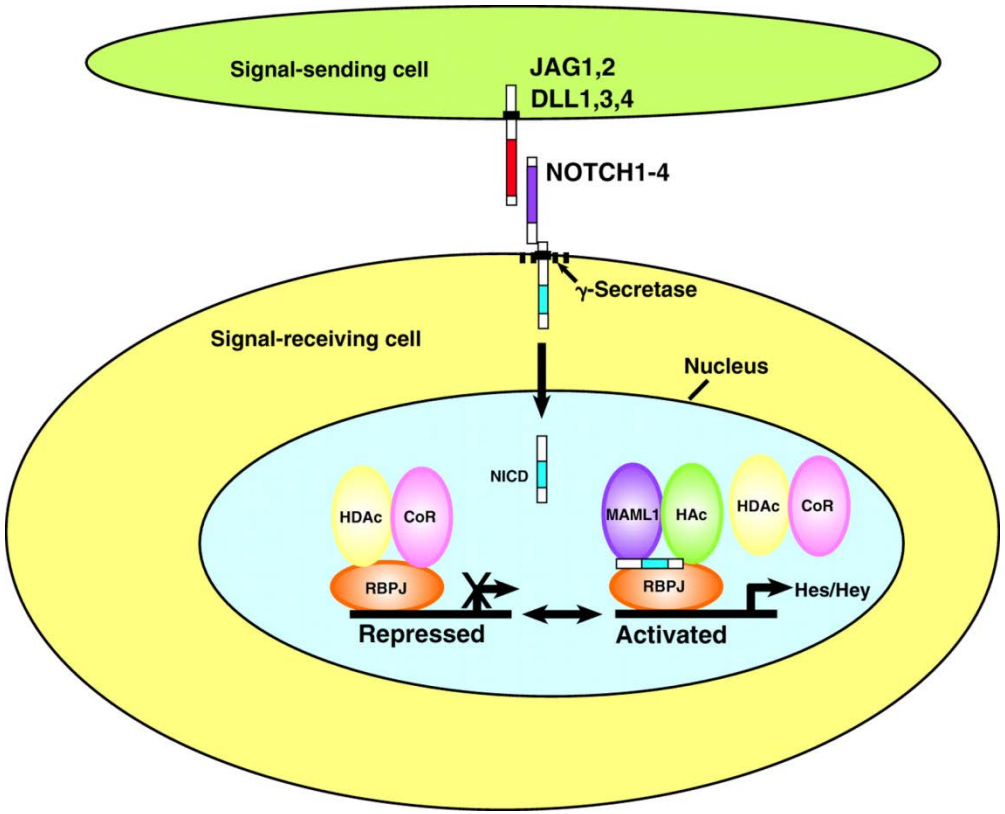
Forced activation of Notch signaling decreased SCLC growth in a transgenic mouse model

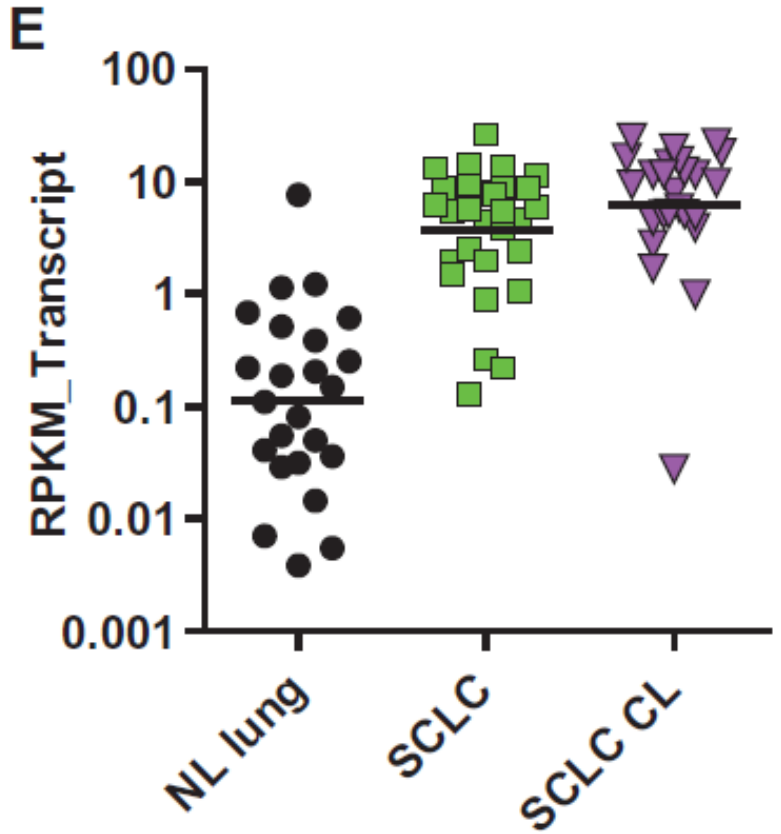




George et al. Nature 2015;524(7563):47-53

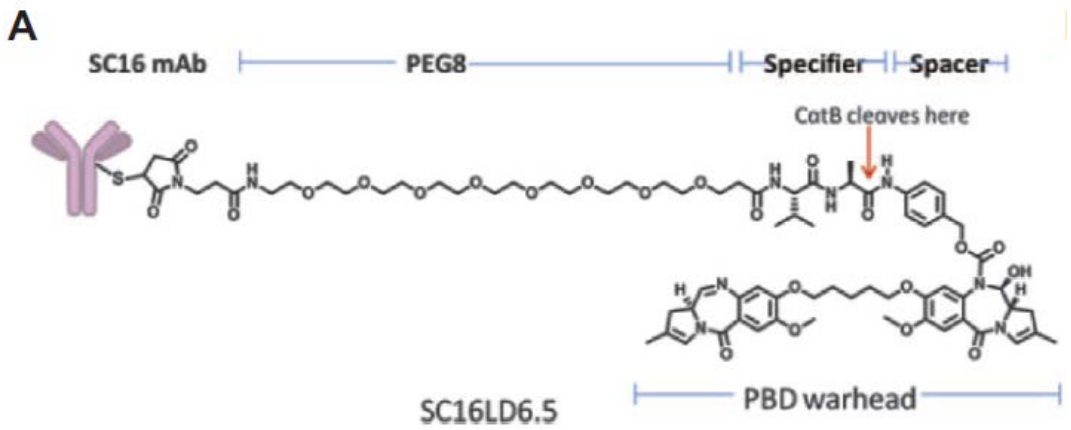
Overexpression of DLL3 in SCLC



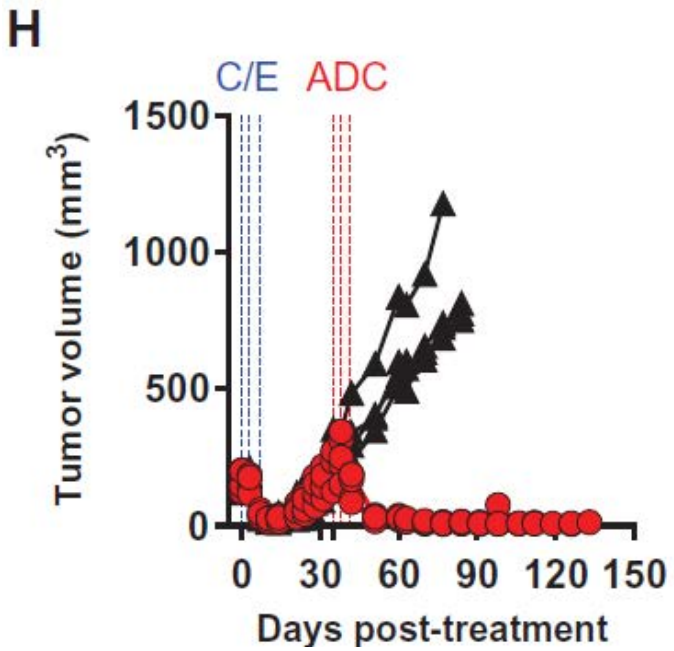


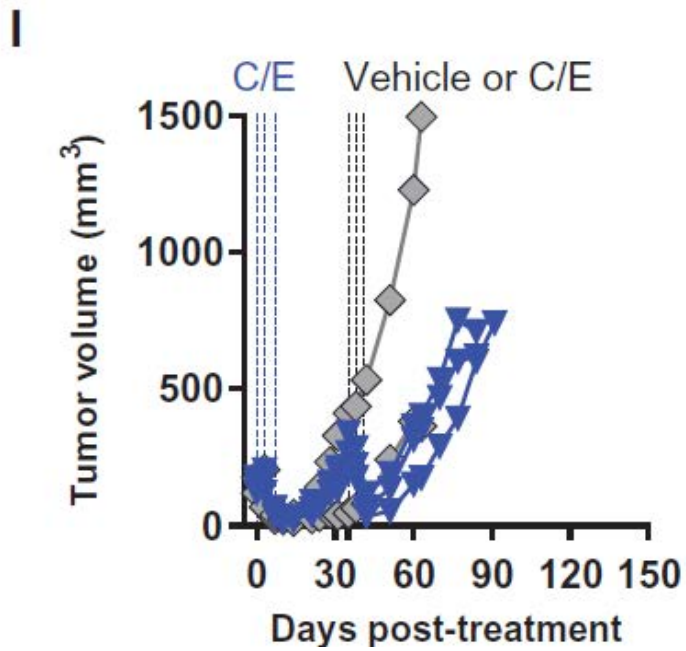
Saunders LR et al. Sci Tranl Medicine 2015

Rova-T: a DLL3 targeting antibody-drug conjugate



rovalpituzumab tesirine (*Rova-T)*





Saunders LR et al. Sci Tranl Medicine 2015

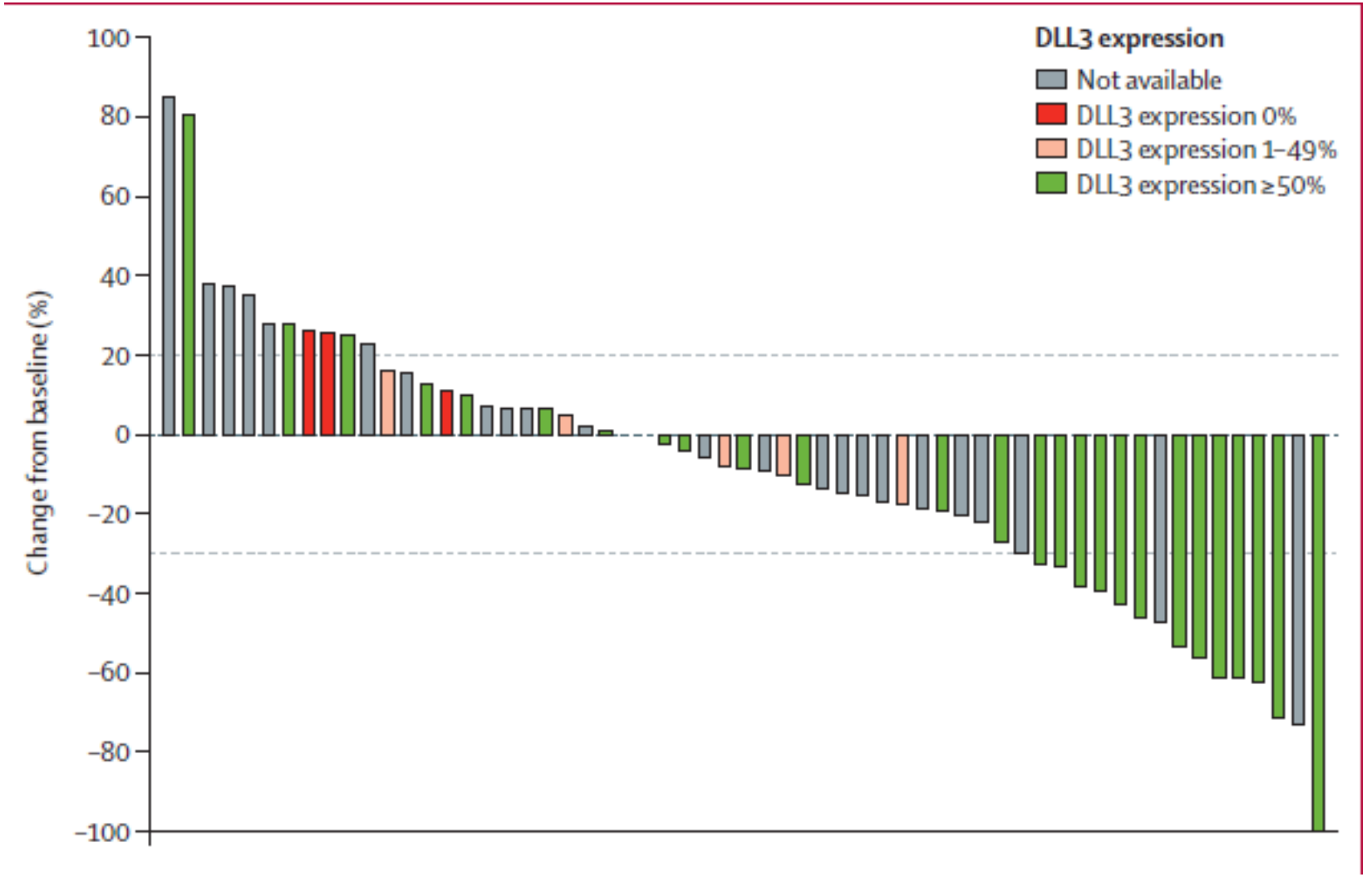
Subject Baseline Characteristics (n=74)

Characteristic	Number (%)
Median Age, years (range)	61 (38-81)
Female	32 (43%)
Baseline ECOG: 0 / 1 / 2	21 (28%) / 50 (68%) / 3 (4%)
Extensive Disease at Presentation	56 (76%)
Response to 1st line therapy	
Sensitive[1]	39 (53%)
Resistant[2]	23 (31%)
Refractory[3]	7 (9%)
Not evaluable	5 (7%)
Treatment-Free Interval (before 2nd line)	4.1 months (0.2-89.1)
Hx CNS mets (Per Investigator)	21 (28%)

Characteristic	Number (%)
Prior Lines of Therapy: 1 / 2	39 (53%) / 35 (47%)
Prior treatments	
Platinum/Etoposide	71 (96%)
Platinum/Other	5 (7%)
Platinum/Etoposide/Other	7 (9%)
Topotecan	8 (11%)
Temozolomide	10 (14%)
ABT-888	8 (11%)
Radiation	61 (82%)
Other	16 (22%)
Tumor DLL3 Expression (any intensity):	
≥ 1% of tumor cells	42/48 (88%)
≥ 50% of tumor cells	32/48 (67%)

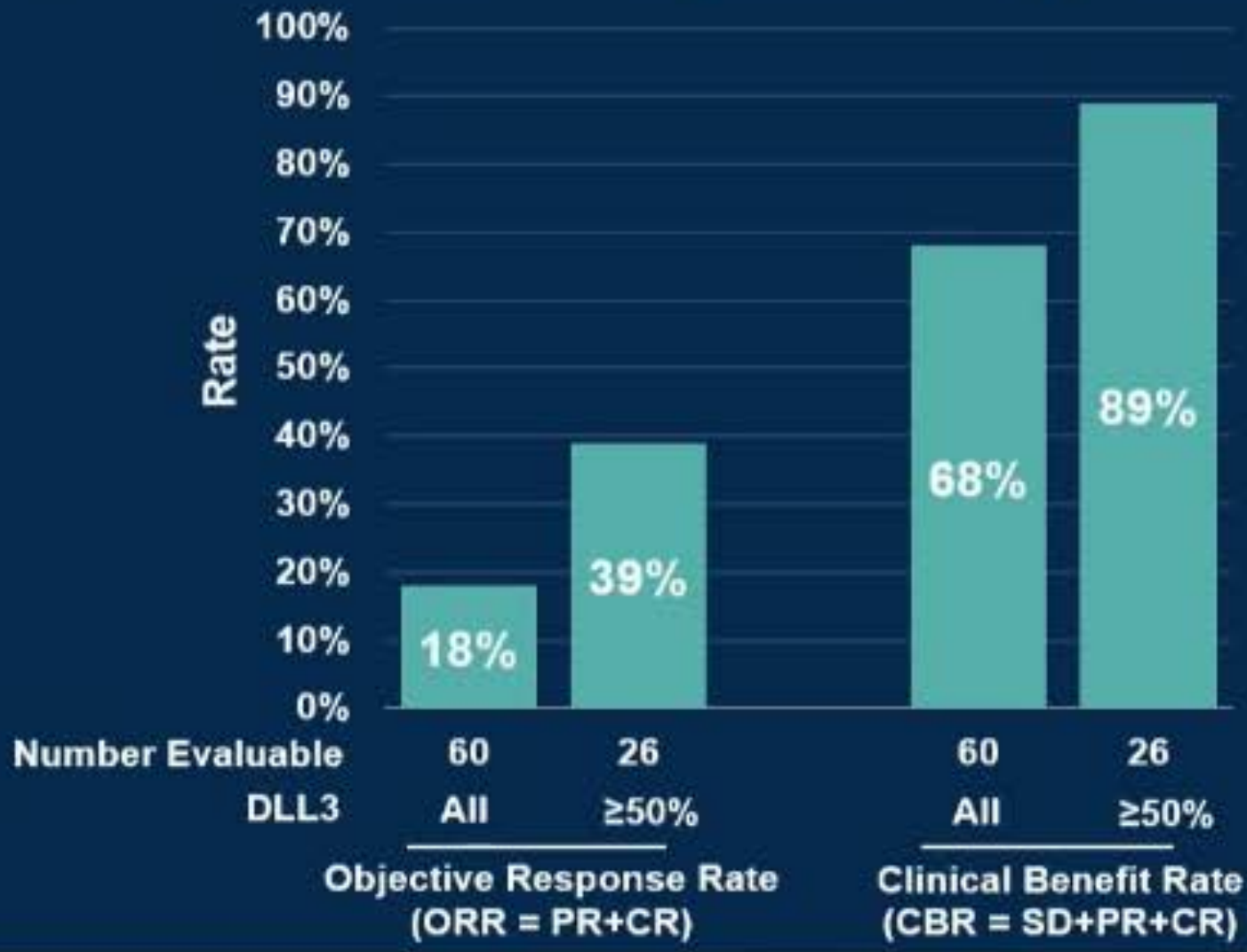
[1,2] Best response of SD or better to 1st line therapy, and 1st-2nd line TFI [1]≥ 90 days or [2]<90 days.
[3] Best response of PD to 1st line therapy.

Waterfall plot showing best change in tumor burden from baseline at active treatment doses (N=60)



Rudin et al. Lancet Oncology 2017, 18:42-51

RECIST Confirmed Responses per Investigator



Response-Evaluable Subjects
Active Doses (0.2-0.4 mg/kg)

C Rudin 2016 ASCO: LBA8505

Phase II result of Rova-T

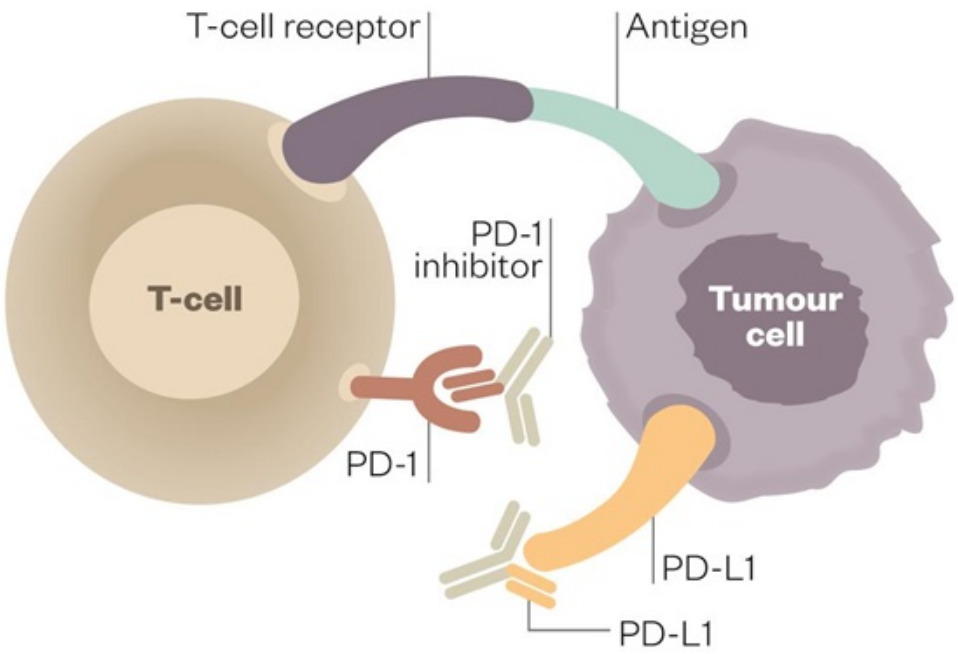
Summary of Investigator Assessed Best Overall Response Rate, Independent Review Committee (IRC) Assessed Objective Response Rate, Duration of Response and Overall Survival in Third-Line SCLC Patients with High DLL3 Expression (N = 177)*

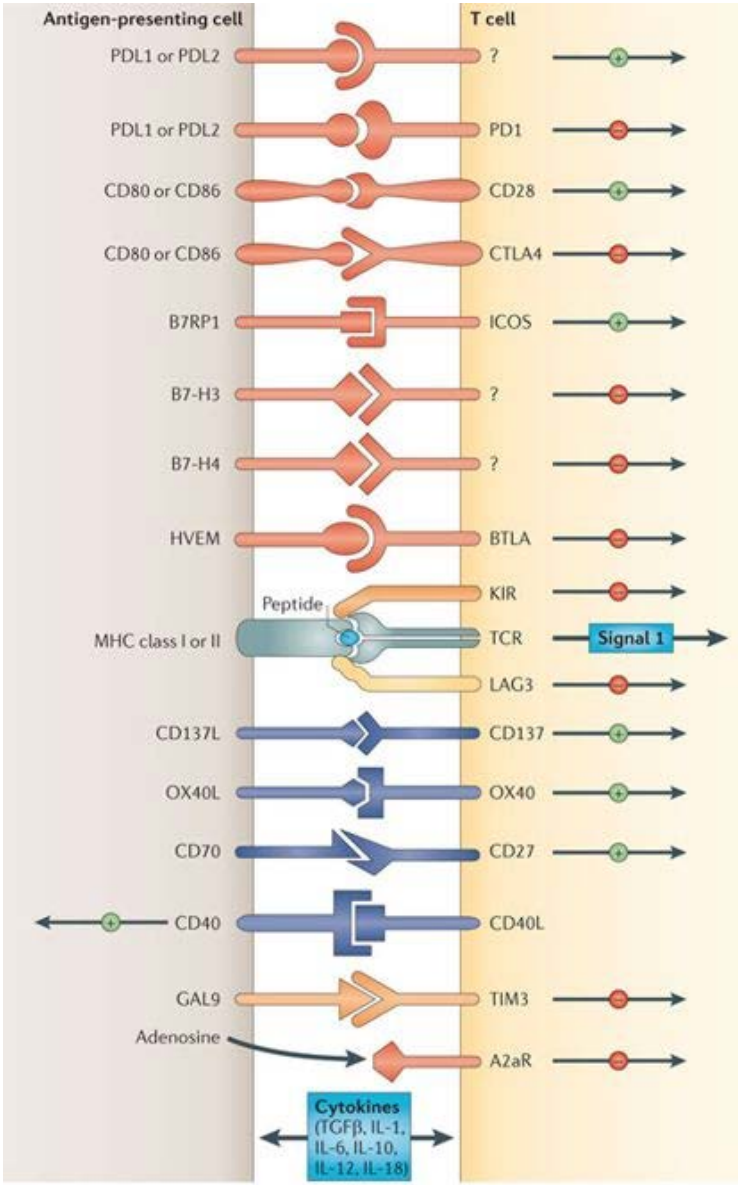
	DLL3 High 3L (N = 177)
Investigator Assessed Outcome	
Best Overall Response Rate[a] (95% CI)	29% (22%, 36%)
IRC Assessed Outcomes	
Objective Response Rate (by RECIST criteria – v1.1)[b] (95% CI)	16% (11%, 22%)
Duration of Objective Response (months) Median (months) (95% CI)	4.1 (3.0, 4.2)
Overall Survival	
Median (months) (95% CI)	5.6 (4.9, 6.8)
Probability of Subjects Alive at 12 months (95% CI)[c]	17.5% (10.8%, 25.5%)

https://news.abbvie.com/news/abbvie-announces-results-from-phase-2-study-evaluating-rovalpituzumab-tesirine-rova-t-for-third-line-treatment-patients-with-dll3-expressing-relapsedrefractory-small-cell-lung-cancer.htm

Immunotherapy in SCLC

Checkpoint Signaling and Immune Activation





http://www.geopolmonitor.com

Nature Reviews Cancer **volume12**, pages252–264 (2012)

Tumor Mutation Burdens in different cancers

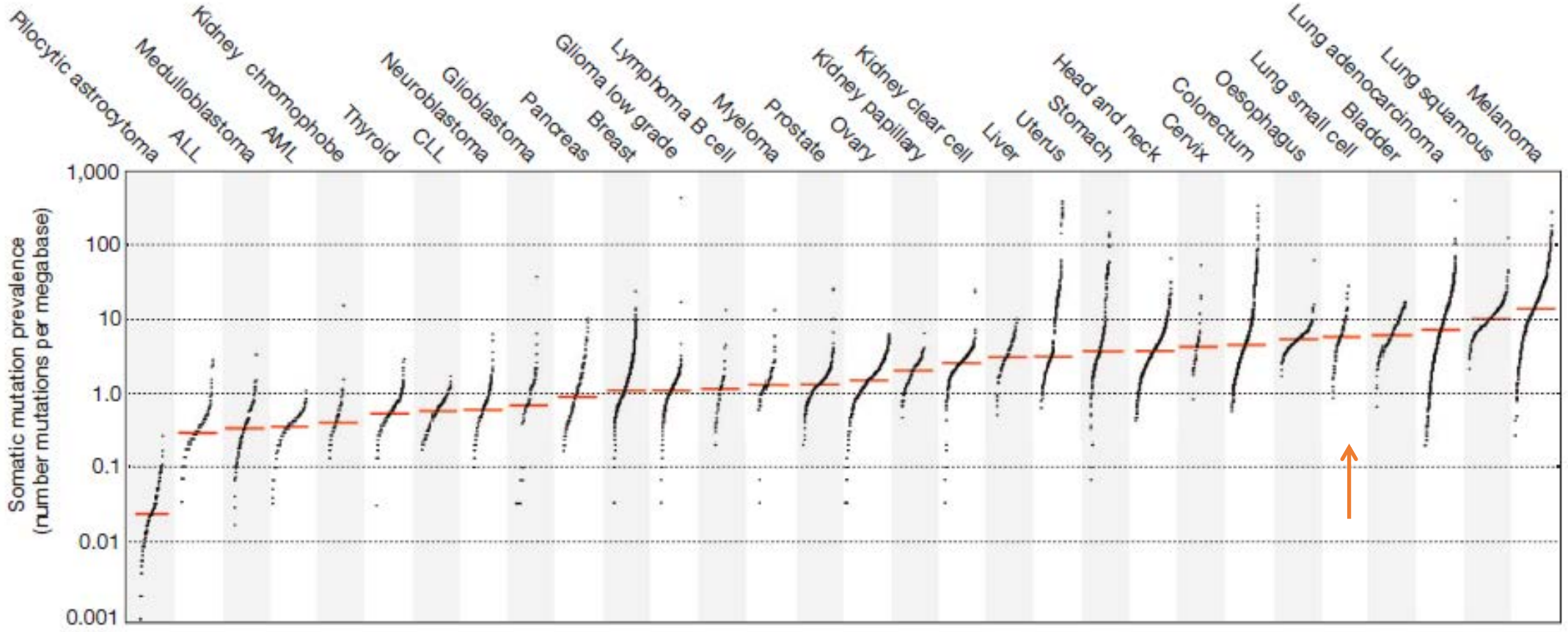
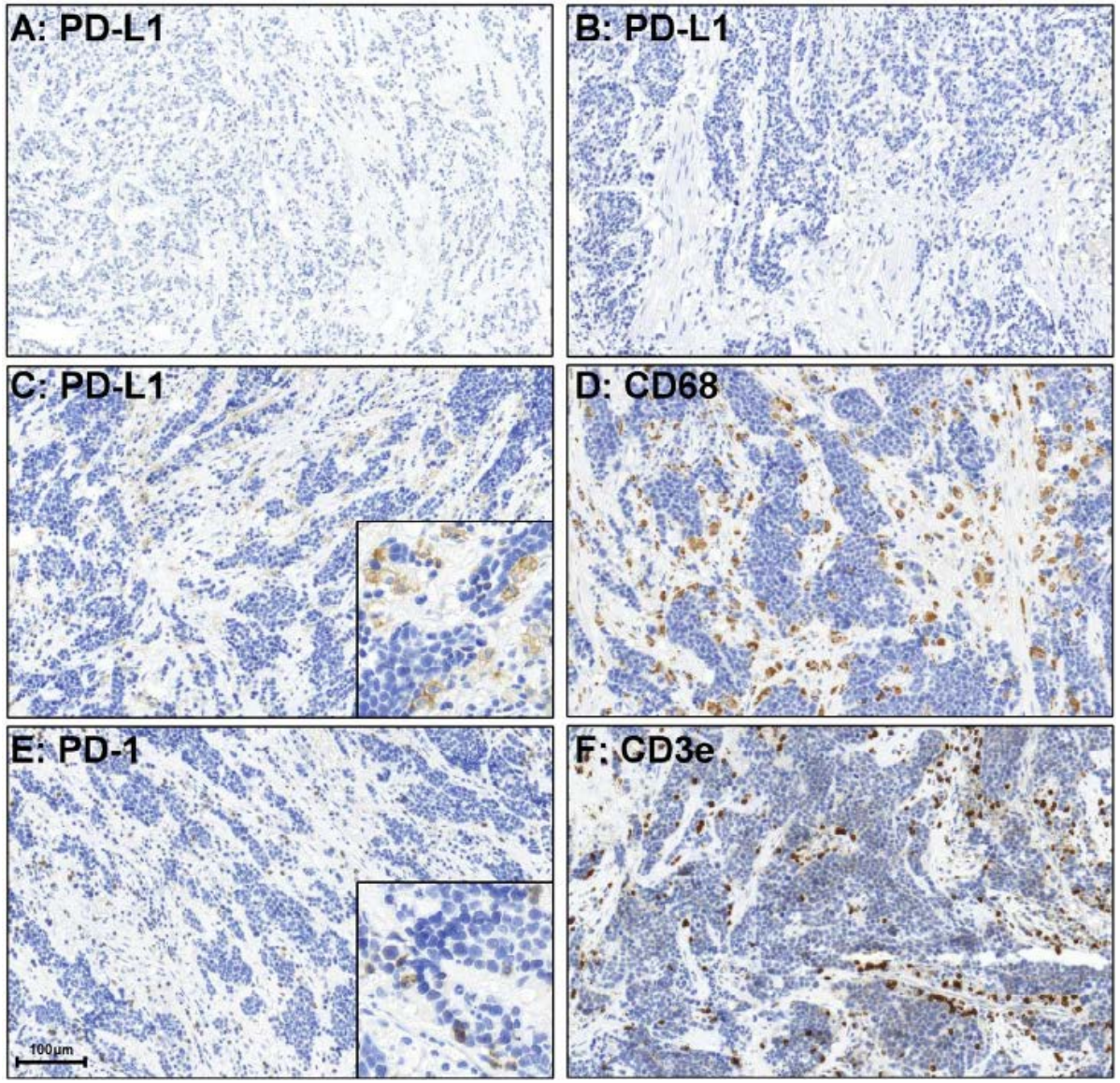


Figure 1 | The prevalence of somatic mutations across human cancer types. Every dot represents a sample whereas the red horizontal lines are the median numbers of mutations in the respective cancer types. The vertical axis (log scaled) shows the number of mutations per megabase whereas the different cancer types are ordered on the horizontal axis based on their median numbers of somatic mutations. We thank G. Getz and colleagues for the design of this figure[26]. ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CLL, chronic lymphocytic leukaemia.

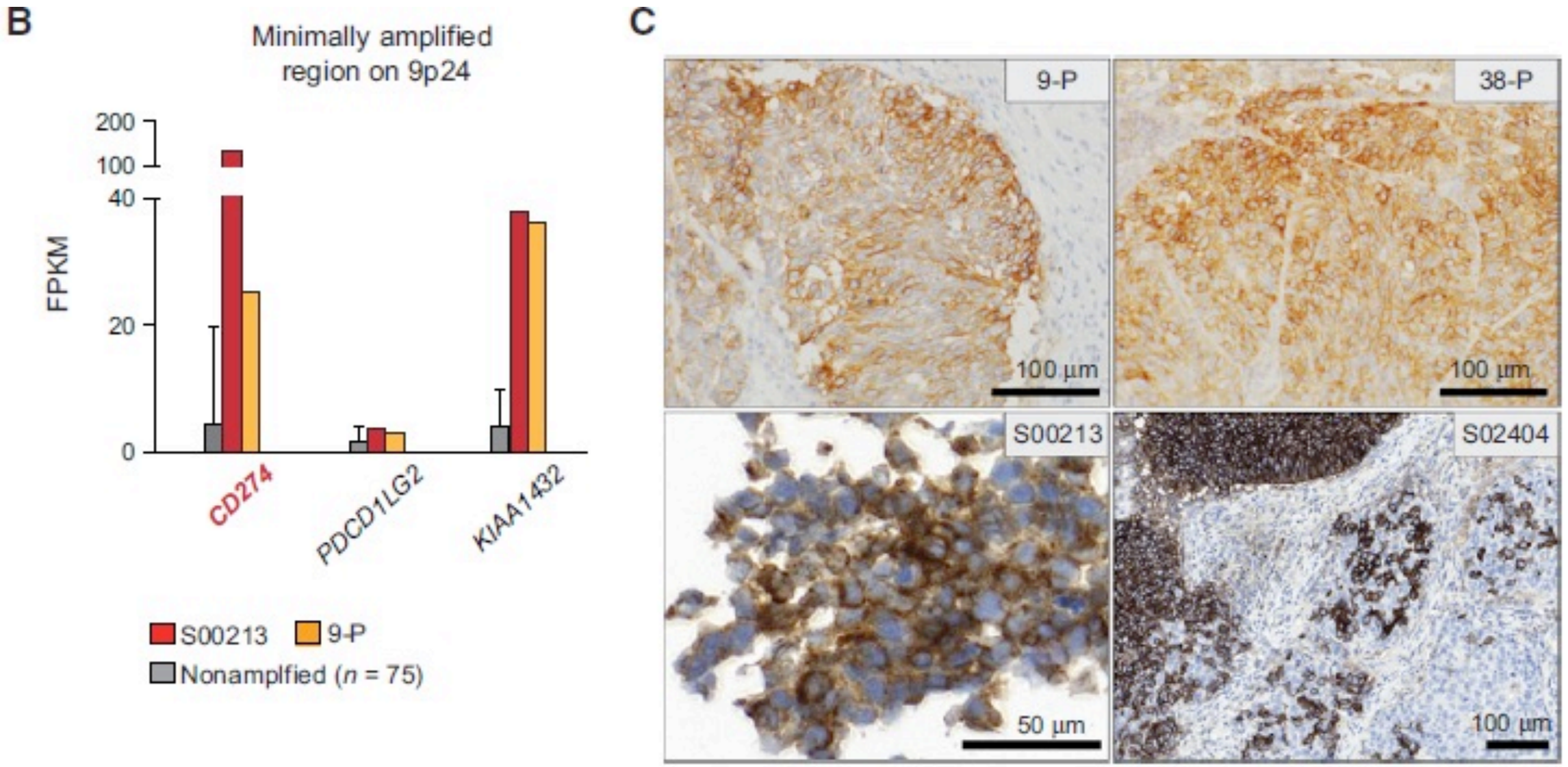
Alexandrov LB, Nature 2013

PD-1 and PD-L1 are expressed in the tumor stroma of small cell carcinoma in a small subset (18.5%) of patients



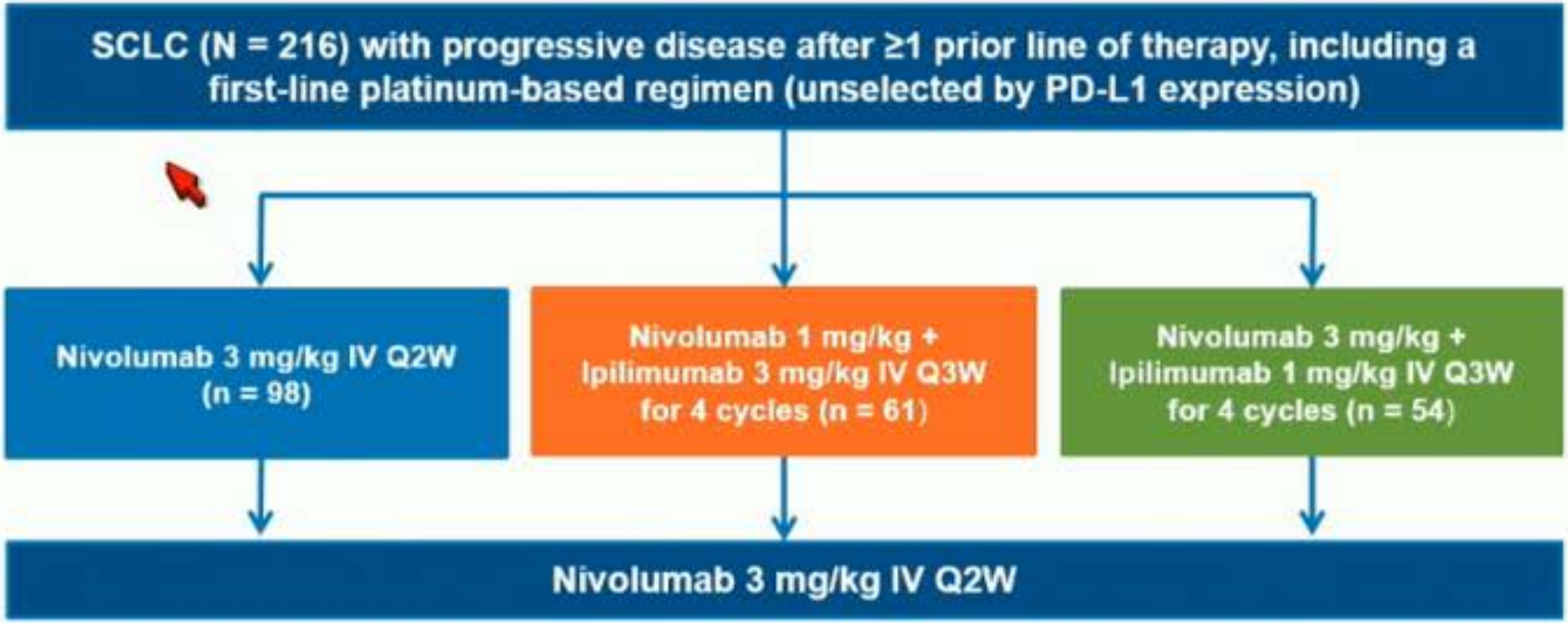
Schultheis AM, et al. European J of Cancer (2015)

CD274 (PD-L1) gene is amplified in 1.9% of SCLC



George et al. Clinical Cancer Research 2017, 23(5):1220-6

Nivolumab +/- Ipilimumab in Recurrent SCLC: CheckMate 032 Study Design



Antonia S et al. 2016 ASCO: abstr 100

Nivolumab +/- Ipilimumab in Recurrent SCLC: Baseline Patient Characteristics

	Nivolumab-3 (n = 98)	Nivolumab-1 + Ipilimumab-3 (n = 61)	Nivolumab-3 + Ipilimumab-1 (n = 54)
Median age, years (range)	62.5 (45–81)	66.0 (37–84)	61.0 (34–74)
Male, %	62	57	59
Race, %			
White	93	98	96
Black/African American	3	2	0
Other	4	0	2
Prior treatment regimens, %			
1	41	52	43
2–3	56	38	52
>3	3	10	6
Current/former smoker, %	97	93	89
PD-L1 expression level,%			
≥1%[a]	14	24	13
<1%[a]	86	76	88
Not evaluable/missing[b]	30	39	26

[a]Percentage of PD-L1 evaluable patients; [b]Percentage of all patients in cohort

Antonia S et al. 2016 ASCO: abstr 100

	Nivolumab 3 mg/kg (n=98)	Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (n=61)	Nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (n=54)
Objective response; 95% CI	10 (10%; 5–18)	14 (23%; 13–36)	10 (19%; 9–31)
Best overall response			
Complete response	0	1 (2%)	0
Partial response	10 (10%)	13 (21%)	10 (19%)
Stable disease	22 (22%)	13 (21%)	9 (17%)
Progressive disease	52 (53%)	23 (38%)	29 (54%)
Unable to determine	12 (12%)	8 (13%)	6 (11%)
Not reported	2 (2%)	3 (5%)	0
Time to objective response (IQR), months	2·0 (1·3–2·8)	2·1 (1·4–2·8)	1·4 (1·3–2·7)

Data are n (%) unless otherwise stated. All patients were enrolled at least 90 days prior to database lock.

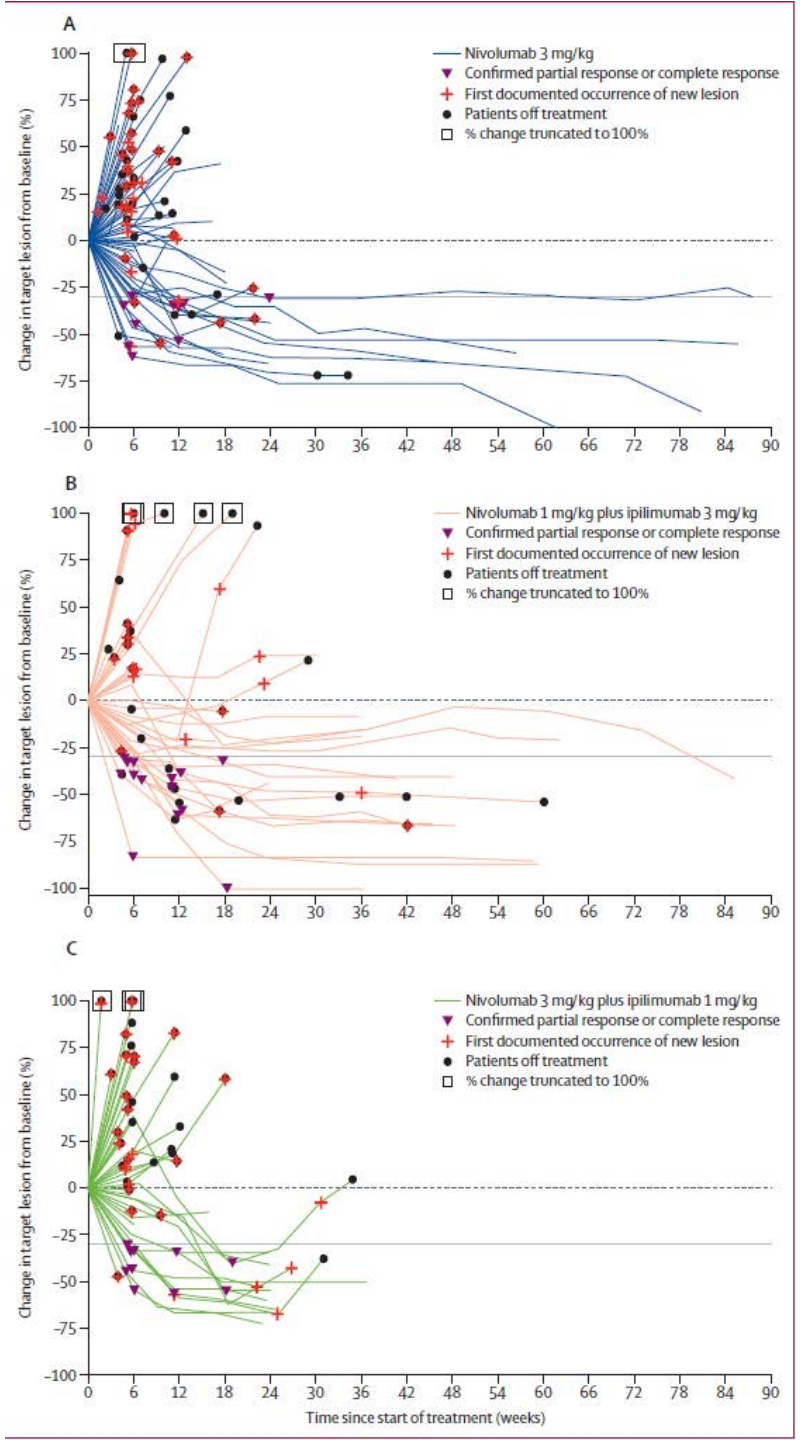
Table 2: **Tumour response**

Antonia S. et al. Lancet Oncol. 2016;17(7):883-95.

Nivolumab 3 mg/Kg

Nivo 1 mg/kg + Ipi 3 mg/kg

Nivo 3 mg/kg + Ipi 1 mg/kg



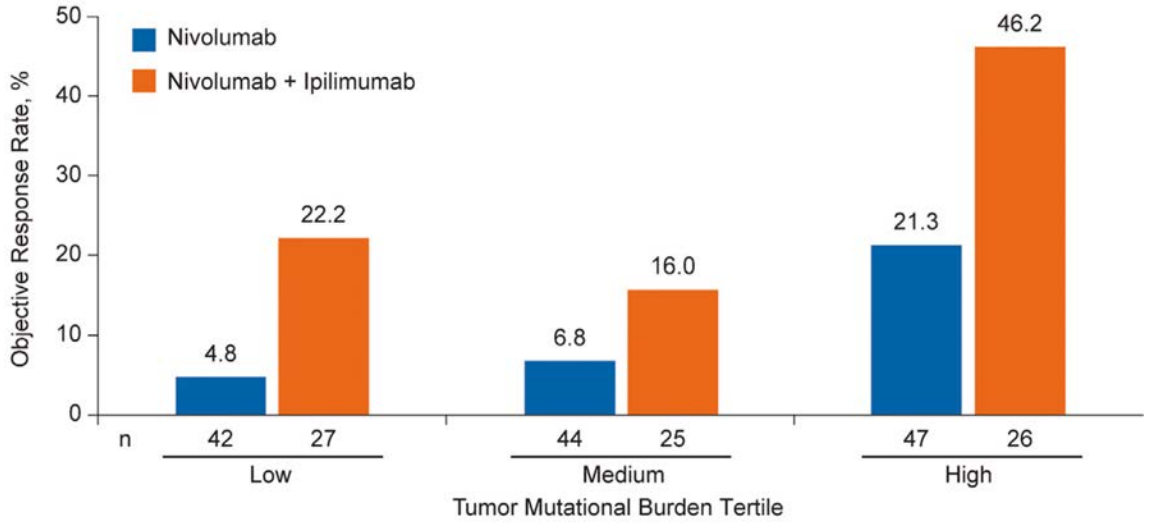
Nivolumab +/- Ipilimumab in Recurrent SCLC: Treatment-Related AEs in ≥10% of Patients

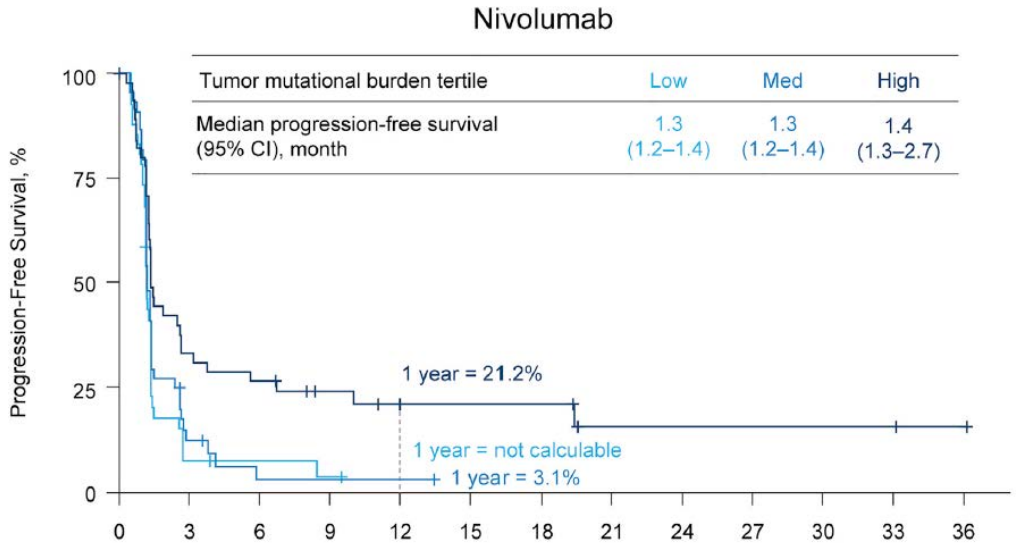
	Nivolumab-3 (n = 98)		Nivolumab-1 + Ipilimumab-3 (n = 61)		Nivolumab-3 + Ipilimumab-1 (n = 54)	
	Any grade, %	Grade 3–4, %	Any grade, %	Grade 3–4, %	Any grade, %	Grade 3–4, %
Total treatment-related AEs	**53**	**13**	**79**	**30**	**74**	**19**
Fatigue	11	1	26	0	22	0
Pruritus	11	0	20	2	9	0
Diarrhea	7	0	21	5	17	2
Nausea	7	0	11	2	7	0
Decreased appetite	6	0	7	0	11	0
Hypothyroidism	3	0	16	2	7	0
Hyperthyroidism	2	0	11	0	6	0
Rash	2	0	20	3	7	0
Rash, maculopapular	1	0	13	3	4	0
Lipase increased	0	0	11	8	0	0
Treatment-related AEs leading to discontinuations	**6**		**11**		**7**	

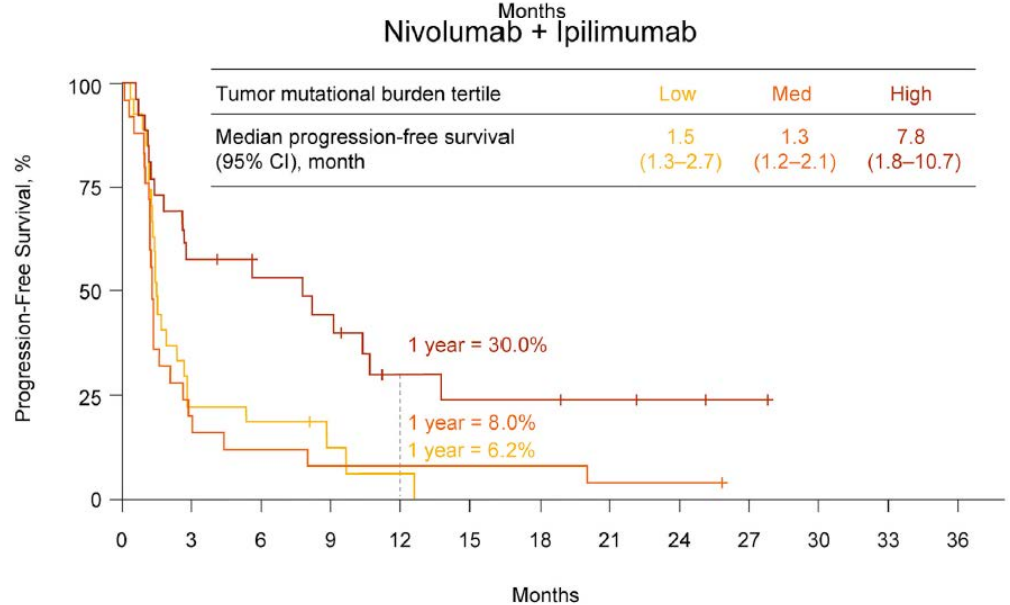
- Two treatment-related deaths occurred in the nivolumab-1 + ipilimumab-3 arm: one due to myasthenia gravis and one due to worsening of renal failure. One treatment-related death due to pneumonitis occurred in the nivolumab-3 + ipilimumab-1 arm
- Treatment-related limbic encephalitis was reported in 2 (1%) patients; 1 case resolved, and outcome for 1 case was not reported
- Treatment-related pneumonitis occurred in 8 (4%) patients; 6 cases resolved, outcome for 1 case is unknown, and 1 case was fatal

Scott A et al. 2016 ASCO: abstr 100

Tumor mutation burden is a potential biomarker to predict response to anti-PD1 therapy







Hellmann, et al. Cancer Cell 2018

Extrapulmonary small cell carcinoma (EPSCC)

Table 1
Frequency of EPSCC per site of origin.

	Percentage of SCC/total per site of origin	Estimated number of patients in US per year*
Pulmonary	15–20%	32,250–43,000
Oesophagus	0.8–2.4%	130–395
Larynx	0.5–1%	60–120
Bladder	0.3–1.0%	200–680
Cervix	±1%	±110
Prostate	±2%	±250
Unknown primary	7–30% of all EPSCC	70–300

SCC denotes small cell carcinoma; EPSCC denotes extrapulmonary mall cell carcinoma.
* http://www.cancer.gov/cancertopics/pdq.

1. EPSCC is a rare group of cancers.
2. First-line systemic chemotherapy for EPSCC is EP doublet.
3. Brain metastasis is rare in EPSCC except for prostate and head & neck SCC. PCI should be decided on an individual basis.

Walenkamp et al. Cancer Treatment Reviews 25:228-236

Summary

- SCLC is a recalcitrant cancer and new therapy is urgently needed.

- Inactivation of TP53 and RB1 is almost universal in SCLC. Other gene mutations may facilitate development and/or growth of SCLC.

- Immune checkpoint inhibitor Nivolumab is recently approved as a third-line treatment for relapsed SCLC. Other novel therapies are being developed.

Questions?